FROM THE MASS RADIOGRAPHY CENTER OF THE ROYAL MEDICAL BOARD,
STOCKHOLM, SWEDEN
(Head: Professor Carl Wegelius)

THE OBSERVER ERROR IN MULTIPLE INTERPRETATION OF PHOTOFLUOROGRAMS

By

HANNS J. BAUER

EJNAR MUNKSGAARD

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TRANSLATED BY
STANLEY H. VERNON

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AB Gustaf Lindströms Boktryckeri
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Preface

With the increased use of the photofluorographic procedure for mass surveys in the field of preventive medicine, both the technique and the diagnostic evaluation of photofluorograms have to meet stringent requirements. The importance of the observer error due to overlooking or misinterpretation of active pulmonary lesions, and the resulting loss of significant diagnoses, have long been known and have been subjected to detailed investigations.—Dual reading of photofluorograms has been considered essential and, in many places, it has been introduced with the aim of reducing the error arising from the human factor, thus increasing the yield and the reliability of photofluorographic diagnoses in mass examinations. The effectiveness of multiple interpretation is dependent, however, on the standards of evaluation and on the readers' perspicacity.—The investigation reported here was designed to elucidate the magnitude of the observer error in multiple interpretation as well as the possibilities of improving the diagnosis.

The investigation was conducted at the Mass Radiography Center of the Royal Medical Board, Stockholm, in cooperation with the City of Stockholm Central Dispensary. I am deeply indebted to my chief, Professor Carl Wegelius, for all his support during the work and for his valuable counsel and stimulating discussions. Professor Erik Hedvall, Head of the Chest Clinic at Uppsala, has been kind enough to take an interest in the study, and I have to thank him too for very helpful discussions. To Dr. Carl Gentz, Medical Director of the Central Dispensary in Stockholm, I am greatly obligated for his interest and encouragement. In the conduct of the test and evaluation of the results, Professor Gösta Ekman, of the Department of Psychology, University of Stockholm, gave me much sound advice, which it is a pleasure to acknowledge here.

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Hanns J. Bauer

Introduction

The principal aim of photofluorographic examination is to detect intrathoracic diseases, for which purpose the method has been employed for nearly two decades. It has established itself as a valuable diagnostic aid in the control of, notably, pulmonary tuberculosis, and has been applied for mass survey.

Parallel with the generally increased use of photofluorography, its diagnostic worth and reliability have been critically analyzed. Since the method may be regarded as a variant of the conventional roentgenographic technique, these investigations have been primarily concerned with technical considerations such as quality and size of the images, reproduction of details, etc.

Since the photofluorographic procedure conforms, in principle, to the same laws as roentgenography, the results of the examination are dependent essentially on these two factors:

(1) The technical equipment and hence the quality of the photofluorographic image, which enables lesions to be visualized.

(2) Reading and evaluation of the photofluorogram and the pathologic changes reproduced thereon.

With the continuous improvement of the photofluorographic equipment and quality, the method has been developed to a point where it satisfies rigorous desiderata as to quality of the image. In point of fact photofluorography today seems to differ, in the diagnostic sense, from roentgenography only in its lesser ability to reproduce details. This drawback is due to the much smaller dimensions of photofluorograms and is not of any major importance relative to the possibility of identifying lesions. In the opinion of many authors, therefore, roentgenography and photofluorography are virtually equivalent in this respect.

On investigation and comparison of the reliability of various roentgenologic methods and photofluorography, it nevertheless emerged that the objectivity in interpretation of the same or different images might vary considerably with different readers as regards the identification of pathologic changes. This served to focus attention on the proficiency and dependability of the interpreters in reading both photofluorograms and roentgenograms. It seemed more difficult to assess the influence of the human factor on the diagnostic reliability of the results than to analyze measurable technical errors of method.

Some investigations were conducted with test series, and not only did substantial discrepancies emerge between the results of different interpreters of the same test material, but one and the same interpreters showed inconsistencies on repetition of the same test. When a similar state of affairs was even observed among experts, faith in the diagnostic dependability of the single interpreter began to subside. It was found that as long as no standardized reading procedure existed which guaranteed an adequate evaluation of all photofluorograms in a given series, it was impossible to demonstrate conclusively the superiority of any particular roentgenologic technique.

Yet on the other hand it does not seem possible, either with the roentgenographic or the photofluorographic technique, to ensure images that will invariably enable different readers to arrive at identical, unambiguous, and above all adequate, interpretations. This poses a substantial problem in judging the effectiveness of individual readings.—The reliability of the photofluorographic method is accordingly dependent not only on technical factors, but also on the alertness and perspicuity of the interpreters.

Discrepancies between the findings of several different interpreters evaluating the same photofluorogram will inevitably cast doubt on the correctness of the diagnosis and reliability of the readers. This holds good regardless of the technical conditions obtaining. The probability of one or the other diagnosis being erroneous depends largely upon how the majority of the interpreters evaluate the same image. Yet the possibility always exists that one of them alone has made the adequate diagnosis. Only on the assumption that all interpreters are equally capable can a uniform and adequate evaluation of all photofluorograms be expected. As long as different interpretations of the same photofluorograms are encountered, it is justified to regard the human factor as a source of error.

The aim of the present investigation was to elucidate the significance of this human source of error in mass photofluorographic surveys. The study is based on constant technical standard conditions during photofluorography of the relevant material.

With the aid of various photofluorographic series evaluated by the staff of readers at the Mass Radiography Center of the Royal Swedish Medical Board, the discrepancies between different interpreters in their opinions and evaluations of pathologic findings, and their mutual criticism while cooperating in dual reading, will be illustrated from diverse points of view.

In addition, a test will be reported that related to the effectiveness of different reading methods with respect to the detection of a number of clinically significant cases, in which the diagnoses were verified by clinicopathologic methods of examination outside the domain of roentgenology. Lastly, the possibilities of improving the diagnoses in future photofluorographic examinations will be discussed.

CHAPTER I

Review of Literature

The literature on photofluorography has been steadily expanding ever since De Abreu introduced the method in 1936 and reported his experience two years later. With the possibility of examining the thoracic organs by an economical and reliable procedure, mass surveys had to be viewed in the light of new considerations of preventive medicine. A number of authors enthusiastically presented their results with the new method and discussed the chances of detecting, with its use, other pulmonary diseases than tuberculosis (HOLFELDER, 1938; BERNER, 1938; HEGGLIN & ZUPPINGER, 1946; BOUCOT, 1955, and others).

No hesitation was felt, however, as to the status of photofluorography in relation to the other roentgenologic methods: The final diagnosis and the verification of photofluorographic findings were reserved exclusively for roentgenology. Photofluorography was accordingly appreciated only for its value in mass surveys, where it was considered to yield satisfactory results (HEGGLIN & ZUPPINGER, 1946, and others).

This outlook was attributable to certain differences in principle that distinguished the photofluorographic from the roentgenologic method:

(1) The miniature image, and hence poorer reproduction of details.

(2) The shorter focus-screen distance and the resulting change in projections.

(3) The light absorption of lens optics, with its influence upon the reproduction of contrast.

(4) The coarse grain of the screen and of the photofluorographic film, which on the miniature image limits the sharpness of details.

De Abreu used 35 by 35 mm film (giving an image of 24 by 24 mm), which at the outset was generally employed in both Europe and America (JANKER, 1938; HOLFELDER, 1938; GRIESSBACH, 1939; SAYÉ & CAUBARRIER, 1939; BRANSCHEID, 1940; GILSON & LAMY, 1941; AXÉN, 1942; HILLEBOE, 1943). In the U.S.A. the desirability of larger sizes was chiefly advocated by POTTER, who introduced the 4 by 5 inch film. In addition the stereo method with varying photofluorogram dimensions, chiefly 4 by 5 inches, came into use especially in the U.S.A. and Canada (DE LORIMIER, 1942; CHRISTIE, 1942; RICHARDS, 1942). In recent years the 80 by 80 and 70 by 70 mm photofluoro-

gram has been used on an increasing scale both in Europe and the U.S.A., and apparently meets the requirements as to quality.

A greater focus-screen distance was called for by some authours (Lindberg, 1939; Jäderholm, 1942). Attempts were made to increase this distance with the aim of utilizing the central beam for projection of details. This necessitated, however, a radiation output so high as to require an equipment that was too ponderous for mobile units and overloaded ordinary electric mains. With the inception of the fast mirror optics, there are nevertheless prospects of meeting the demand for a greater focus-screen distance.

The light absorption of lens optics influences the reproduction of fine differences in contrast and, for larger images of say 4 by 5 inches, requires high roentgen outputs (Hauser & Dundon, 1945).

The disadvantage of the faster, coarse-grained films may also be lessened by the use of mirror optics in photofluorography. Böhme (1939) pointed out that very small pulmonary foci were more distinct on photofluorograms than on ordinary roentgenograms. He used fast film (32 Scheiner). The speed of a film varies, of course, with its grain. Böhme employed 35 by 35 mm film, giving an image of 24 by 24 mm. The phenomenon reported by Böhme may be attributable to a relatively greater uptake, on the image, of small contrast differences at the cost of detailed reproduction of the contrast-producing object. This state of affairs might also lead to over-diagnosis in some cases, since contrast fusions occur that may resemble pulmonary densities on the photofluorogram.

In the course of time, different photofluorographic apparatus, cameras and film sizes were introduced, enabling their comparative diagnostic effectiveness to be investigated and compared with ordinary roentgenography. Such comparative studies were conducted mostly in the U.S.A. It was first and foremost a question of investigating the agreement between roentgenologic and photofluorographic diagnoses of certain pulmonary lesions (Branscheid, 1940; Plunkett, 1941; Potter, Douglas & Birkelo, 1940; Hauser & Dundon, 1945; Tice, 1946). The degree of concordance found between photofluorographic findings and the roentgenologic diagnosis varied with different authors (Pindell, 1942; Clark, Poulsson & Gage, 1941; Hilleboe, Haas, Palmer & Gardner, 1942; Hilleboe & Morgan, 1945). The difference between the two methods of examination seems to have been greatest, as a rule, in the diagnosis of minimal lesions, which in most cases were overlooked on the photofluorograms.

Birkelo, Chamberlain, Phelps, Schools, Zacks and Yerushalmy (1947) analyzed in their classic test the effectiviness of various photofluorographic procedures and roentgenography in the detection of pulmonary lesions. Their investigation envisaged a comparison of 35 by 35 mm photofluorograms, 4 by 10 inch stereo-photofluorograms, and 14 by 17 inch paper and roentgen film

with respect to their relative value in mass surveys. Each lung image in their test series had been photographed with each of these four methods. On independent reading of the different images, such a substantial inter-individual difference emerged—even in evaluation of 14 by 17 inch roentgenograms—that it seemed impossible with the aid of the roentgenographic diagnosis to assess the relative merits of the various photofluorographic methods in mass examinations. The authors concluded that none of the four methods applied was superior to the others for the detection of such lesions that call for further clinical investigation.

At a second independent reading of the roentgen films by the same interpreters, the diagnoses of identical roentgenograms by the individual interpreters were found to be inconsistent with their initial findings. The uncertainty as to the correctness of diagnoses which had already arisen through inter-individual differences was thus heightened by the intra-individual discrepancy, i.e. that between the same interpreter's diagnoses. Statistical analysis of the frequency of identical evaluations of images photographed with the four different methods showed, moreover, that none of the latter could lay claim to any major reliability or superiority (YERUSHALMY, 1947).

It seemed impossible that different interpreters, working independently of each other, could arrive at a standard evaluation; not even the same reader made identical diagnoses. The inter-individual difference between the diagnoses was conceivably attributable to varying capability of the interpreters. The divergence from an earlier diagnosis by the same interpreter—the intra-individual difference—gave rise to doubt in the ability of the roentgen method always and unequivocally to ensure the same diagnosis.

The reliability of a diagnosis with any of the roentgen methods is apparently dependent, therefore, on two factors—the technical quality of the image and the efficiency of its interpretation—the latter being evidently influenced by a human source of error.

According to GARLAND (1950) the inter-individual variation amounted to 9–24 per cent, and the intra-individual variation to 3–31 per cent. The noteworthy finding in his investigation was that even in extensive pulmonary lesions the diagnoses made by the same or by different interpreters were by no means consistent.

In another investigation, YERUSHALMY, HARKNESS, COPE & KENNEDY (1950) examined the possibility of arriving at a standard reading of photofluorograms. Six interpreters read the same series of photofluorograms (70 mm film, lens optic) independently of each other. All positive photofluorographic findings which they detected and that were considered to require further checking were roentgenographed. Only those photofluorographic findings that all of them were able to identify unambiguously as follow-up cases on the roentgenograms were regarded as "positive"; those which could not be veri-

fied unanimously were classed as "negative". Doubtful cases in which the interpreters failed to reach a uniform evaluation were discarded. This pool of positive photofluorographic findings would in all likelihood, it was thought, contain all positive photofluorograms that existed in the series and which could be expected to receive identical diagnoses by the interpreters. At the repeated independent reading of this series by the same six interpreters, the proportion of cases identified averaged only 68 per cent (range 57–74 per cent).

Similar investigations were conducted by GROTH-PEDERSEN, LØVGREEN & THILLEMANN (1952), HOLM, NIELSEN, MØLLER & WINGE (1954), GRIEP (1955), and OSCARSSON (1954). All results showed that the average efficiency of the interpreters was substantially below 100 per cent, regardless of which photofluorographic technique or which film size had been used.

Even though the discrepancy between different interpreters' diagnoses of the same image chiefly applied to relatively small pulmonary lesions, major importance nevertheless attached to the subjective factor in mass surveys. YERUSHALMY *et al.* (1950), on the basis of their experience, recommended dual reading in view of the greater diagnostic reliability. In their opinion this dual reading could be done either by the same or by another interpreter, the diagnostic gain then amounting to 34 per cent of the cases overlooked at the initial reading. In their tests, moreover, eight "over-diagnosed" cases emerged for every fresh positive case.

In another investigation, YERUSHALMY, GARLAND, HARKNESS, HINSHAW, MILLER, SHIPMAN & ZWERLING (1951) demonstrated a substantial disparity between evaluations of the degree of activity of pulmonary lesions on roentgenograms. Since corresponding evaluation on photofluorograms could be assumed to present greater difficulties, it was worth while, from the clinical standpoint, finding out to what extent clinically verified "active" pulmonary lesions were overlooked in mass examinations. An investigation was accordingly conducted by ZWERLING, MILLER, HARKNESS & YERUSHALMY (1951), who found that "active" lesions were overlooked or judged "inactive" to the same extent.

Summarizing, a very appreciable loss of significant diagnoses must be expected in single reading in mass examinations. Dual reading greatly enhances the reliability of the photofluorographic diagnosis, the chances of misdiagnosis or missed diagnosis being correspondently reduced. The degree of activity of a pulmonary lesion cannot in all cases be established from a roentgenogram or a photofluorogram. Hence even apparently insignificant lesions must be respected, in view of their possible clinical significance, if photofluorographic mass surveys are to satisfy the desiderata to which the method is subject.

Personal Investigations

Introduction

The aim of the present study was to investigate the reliability of photofluorographic diagnosis with respect to pulmonary diseases. The effectiveness of various dual reading methods will here be compared, with due regard to influence of individual factors that may affect the results of photofluorogram readings. The degree of concordance between the photofluorographic diagnosis and the final clinical evaluation of photofluorographically detected pulmonary lesions will be examined according to principles that may be of some importance in appraisal of photofluorography in mass surveys from the standpoint of preventive medicine.

The influence of dual reading on the results of different interpreters will be illustrated in two ways. First the results in a major series of photofluorograms, subjected to dual reading by fourteen physicians, will be presented. The mutual criticism, and the modification of the initial results after the second reading, will be described with respect to the inter-individual difference, i.e., that between readers equally qualified and working under identical technical conditions and on identical principles. The bearing which this inter-individual difference in photofluorogram reading has upon the diagnostic reliability will then be examined in the light of the results in a test material evaluated by eight of the fourteen physicians who had acted as interpreters in the major series.

The test material was so evaluated that the results not only demonstrate the magnitude of the inter-individual difference and the correction of misinterpretations through various dual reading methods, but also make it possible to estimate the intra-individual variation when a single reader evaluates the same photofluorograms repeatedly. The significance of this intra-individual variation will be analyzed further in the discussion on the observer error in photofluorogram reading.

CHAPTER II

Material and Methods

Material

In this investigation the material was as follows:

(I) General photofluorographic material from mass surveys in Sweden.

(II) Selected photofluorographic material for test purposes.

Finally the readers of the photofluorographic material will be discussed.

I. General Photofluorographic Material

This general material derives from mass surveys carried out in Sweden under the direction of the Mass Radiography Center of the Royal Medical Board (hereinafter called the Center) and local public health authorities during the period from 1953 to 1956. It comprises 2,084,583 photofluorograms, dual readings of which had been done by fourteen physicians working, during that period, at the Center. The population studied was composed of all age groups from 10 years upwards, with a roughly equal sex distribution. Since, in Swedish mass surveys, the attendance averages about 90 per cent of those summoned for examination, the social grouping in this material should approximate that of the total population. The material includes, moreover, populations in different parts of Sweden where mass surveys were conducted.

This general photofluorographic material will be investigated with respect to those discrepancies between the initial evaluations of the fourteen physicians which emerged on mutual correction of over- and under-diagnoses after the dual readings. Further, the inter-individual difference found when the interpreters themselves checked and corrected each other's initial results will be illustrated.

These inter-individual differences in the evaluation of pathologic findings accordingly relate only to photofluorographic diagnoses of pulmonary lesions which the Center reported as follow-up cases to the relevant central dispensaries.

II. Photofluorographic Material for Test Purposes

This series is a selected part of the general material, and was used for test evaluations by eight of the fourteen physicians. It comprises 3,268 pulmonary photofluorograms in antero-posterior and lateral projections, distributed

among 100 film rolls. It derives from the second mass survey in the City of Stockholm during 1955 and 1956.

The test material consists of two sections:

(1) Test photofluorograms (Test cases).

(2) Other photofluorograms.

This material was selected on the basis of considerations that will be described in the following.

In planning the investigation special attention was given to selection of the test material, its composition having to meet certain requirements.—In relatively small test series of photofluorograms to be evaluated by one or more interpreters, the results may be influenced by certain random factors such as indisposition, psychologic factors, etc. In this way the conclusions drawn may be misleading.—Hence it was decided to take a test material of such scope that its analysis, both on independent initial reading and on re-evaluation, would take a considerable time for the interpreter. The tests could thus be likened to a critical appraisal of individual evaluations over a certain observation period. This period totalled at least one month per interpreter.

In selecting the test cases it was required that the lesions not only should be identifiable on photofluorograms and verifiable on follow-up roentgenograms, but should be of such clinical significance as to prompt immediate therapeutic measures on the basis of the verified diagnosis. A further desideratum was that the test cases should constitute morbid processes originally detected photofluorographically and diagnosed by a member of the team on some earlier occasion (about one to two years before the investigation opened). It was plausible to assume that these lesions should be recognized once more during the test and, as before, evaluated as follow-up cases. Since the essential purpose of photofluorographic examination is to detect these clinically significant cases, it was of interest to elucidate the probability of their re-detection and diagnosis. This applied especially to mild or doubtful pulmonary lesions that were difficult to evaluate.

Great importance was attached to the composition of the material, so that the test conditions would conform, as far as possible, to the daily routine work at the Center. The test material had to be similar to an ordinary material from a mass survey. Hence, efforts were made to avoid an "unnatural" concentration of test cases that might have specially alerted the interpreters or caused other reactions on their part. The test cases were accordingly dispersed as "random samples" in a ratio of one case to approximately thirty photofluorograms, this naturally being unknown to the interpreters. Such a "normal" film roll thus included other randomly distributed "follow-up cases" that would also confront the interpreter with diagnostic problems. The evaluation would therefore be made without cognisance of the difference between "test cases" and other follow-up cases.

This arrangement of the test material virtually eliminated the chances of the original composition of the entire material being reproduced, with regard to the clinical diagnoses and significance of these other follow-up cases. Their evaluation during the investigation, and their probable clinical significance, are of subordinate importance in this connection. However, their identification as follow-up cases on final evaluation of the entire test material by the different interpreters will be reported.

The photofluorographic material derives from the second mass survey of the population of Stockholm in 1955 and 1956. During this period examinations were carried out, block by block, in virtually every part of the city. The population examined comprised males and females of all ages from 16 upwards. The number attending for photofluorographic examination, which was performed by mobile units from the Royal Medical Board, amounted to 270,292, or 68 per cent of those summoned. The age and sex distribution is tabulated below.

Table 1. Age grouping of population examined during the surveys of 1949–1951 and 1955–1956 in Stockholm.

Age groups	Males: Number examined 1949–1951	Males: Number examined 1955–1956	Males: % of examined 1949–1951	Males: % of examined 1955–1956	Females: Number examined 1949–1951	Females: Number examined 1955–1956	Females: % of examined 1949–1951	Females: % of examined 1955–1956
–19	7,170	6,368	4	6	6,909	7,134	4	6
20–29	29,094	16,898	15	11	37,577	20,940	16	13
30–39	45,690	28,118	24	17	51,373	33,346	22	18
40–49	41,832	27,120	22	23	51,386	33,396	22	22
50–59	31,136	19,777	17	24	40,966	26,619	17	22
60–69	22,224	13,461	12	14	30,098	19,957	12	14
70–	11,695	7,144	6	5	16,071	10,014	7	5
Total	188,841	118,886	100	100	234,380	151,406	100	100

The mass chest examinations of 1949–1951 in Stockholm, unlike the above-mentioned survey of 1955–1956, were designed to cover the entire population in the relevant age groups. The figures reveal, however, some similarity in the sex distribution according to age groups. The preponderance of females is attributable to their higher percentual attendance.

1. *The Test Cases*

In order to secure a fairly representative distribution, in the age and sex groups, of the pathologic cases originally detected in the mass survey of 1955 and 1956, the test cases were sampled from the cards filed at the Central Dispensary in Stockholm.

Table 2 shows the age and sex distribution of the test cases and the tuberculosis cases requiring treatment that were detected photofluorographically in 1955 and 1956.

A total of 99 test cases, distributed among 100 film rolls, were selected. Each film roll comprises about 30 chest photofluorograms in antero-posterior and lateral projection. The 99 test cases were accordingly dispersed among a total of 3,268 photofluorograms.

In comparison to the reported normal incidence of follow-up cases in mass surveys of the population of Stockholm (4–5 per cent of the number examined), the test cases made up about 3 per cent of the total photofluorographic material. The material included, however, not only test cases but an unknown number of other pathologic findings; hence it seemed justified in practice to reckon with a normal incidence of follow-up cases in the test material. The clinical diagnoses and the significance of these other follow-up cases are irrelevant here; the latter merely served in some degree to camouflage the test cases, which might have been detected more readily had they been dispersed at closer intervals.

The test cases accordingly represented diagnostically verified pulmonary lesions that were both of clinical significance and constituted newly detected cases of the type which photofluorographic examination could be expected to reveal. Yet it does not follow that these processes were fully manifest, or even sufficed to produce subjective symptoms.—Indeed, precisely the opposite state of affairs is increasingly common in photofluorographically detected cases of pulmonary disease. Hence they are not devoid of clinical significance. —Winge (1956) pointed out that pulmonary tuberculosis cases first detected in repeated photofluorographic surveys of the same population could be largely classified as "minimal cases" according to the N.T.A.* nomenclature, in contrast to other dispensary patients.—Moreover, they seem to have a better prognosis and may be regarded, in some degree, as early diagnoses.

Since the present test cases mostly concerned tuberculosis initially detected during the second mass survey in Stockholm, a similar state of affairs may be expected notwithstanding, for instance, the higher tuberculosis morbidity rate in that city.—Sampling of freshly detected cases from the dispensary material suggested that "minimal lesions" would preponderate among the test cases. This assumption is confirmed by the following.

* See definition on page 19.

Table 2. Age distribution of test cases in relation to the distribution of active pulmonary tuberculosis cases detected in the mass survey of the population of Stockholm during 1955–1956.

Age group	Males			Females		
	Number of active tuberculous cases in need of treatment	Number of test photofluorograms with active pulmonary lesions		Number of active tuberculous cases in need of treatment	Number of test photofluorograms with active pulmonary lesions	
		Tuberculosis	Non-tuberculous etiology (cancer, etc.)		Tuberculosis	Non-tuberculous etiology (cancer, etc.)
–19	2	1	—	3	2	—
20–29	20	7	—	21	8	1
30–39	32	9	1	27	12	—
40–49	53	9	—	22	7	1
50–59	57	9	2	16	5	1
60–69	26	4	6	9	4	1
70–	12	3	3	4	2	1
Total	202	42	12	102	40	5

In the selection of test photofluorograms some non-tuberculous cases, such as pulmonary carcinoma, were included. They are incorporated in the tabulated figures for newly detected cases requiring therapeutic measures.

The clinical diagnoses of the test cases are listed in the tabulation on page 84. The 99 test cases show, with respect to the extent of the pulmonary lesions, the following distribution:

"Far advanced"	4	(4 per cent of the test cases)
"Moderately advanced" . .	30	(31 » » » » » »)
"Minimal"	65	(65 » » » » » »)

This classification* shows, as regards the definition of lesions designated as "minimal", wide limits. The distribution of the present test cases accords, however, with data reported by Oscarsson (1954) and Hilleboe & Morgan (1945).—These cases were classified in conference after the investigation, when it emerged that most of those with "minimal" lesions were apparently well within the definition given by N.T.A. Classification was based solely on the photofluorographic findings.

The implication is that under the present conditions in repeated photofluorographic surveys, attention must be directed to relatively small suspected pulmonary lesions that may be fresh processes which have not had time to reach any major extension. Faith in their tendency to heal spontaneously is incompatible with the aims of photofluorography. In respect of the test cases the material is thus adapted to those demands which the photofluorographic diagnosis has to satisfy.

2. *Other Photofluorograms in the Test Material*

The material comprised a further 3,169 photofluorograms, among which the test cases were distributed. It included a number of positive photofluorographic findings, the clinical significance of which is of less interest here than the degree of concordance between the eight test interpreters in identifying them. They were evaluated according to the same principles as the test cases, for the interpreters were of course unaware of the difference between those cases and the other positive findings. The results with regard to these

* Classification according to the Diagnostic Standards and Classification of Tuberculosis, National Tuberculosis Association, 1955 edition, New York 19, N.Y.

"*Minimal*": slight lesions without demonstrable excavation confined to a small part of one or both lungs. The extent of the lesions regardless of distribution shall not exceed the equivalent of the volume of lung tissue which lies above the second chondrosternal junction or the spine of the fourth or body of the fifth thoracic vertebra on one side;

"*Moderately advanced*": one or both lungs may be involved but the total extent of the lesions will not exceed the following limits: slight disseminated lesions which may extend through not more than the volume of one lung or the equivalent of this in both lungs; dense and confluent lesions which may extend through not more than the equivalent of one-third of the volume of one lung; any graduation within the above limits; total diameter of cavities, if present, estimated not to exceed 4 cm;

"*Far advanced*": lesions more extensive than moderately advanced.

latter reflect in some measure the conditions under which the general material was evaluated, the diagnoses being based solely upon photofluorographic findings.

The Readers

The general material was interpreted by fourteen physicians—eleven males and three females—who were attached to the Center from 1953 to 1956. Their ages ranged from 35 to 70 years and averaged about forty-five. All of them had many years training and experience in the clinical and roentgenologic evaluation and diagnosis of pulmonary diseases. Roentgenologic training predominated in some, clinical training in others. The majority of them also had several years experience with reading of photofluorograms. Some worked at the Center only for a short time or did part-time work there.—The writer himself is a member of the staff at the Center and participated in the reading of the general photofluorographic material, though not, of course, in the present test.

The test material was evaluated by eight physicians who had also taken part in the reading of the general material. Most of them were members of the permanent staff. The mean age in this group, composed of three female and five male physicians, was about 41 years.

Methods

I. Organization and Execution of Mass Surveys in Sweden

The interpretation of the photofluorographic material to which this paper relates was done at the Mass Radiography Center of the Royal Medical Board. Since 1946 the Center has arranged large-scale surveys in all parts of Sweden, and between 1946 and 1956 a total of 4,652,101 persons were photofluorographed by its mobile units.

These mass surveys are conducted in cooperation with local public health authorities. The Center provides portable apparatus and technical staff, who do the photography. Development and reading of the photofluorograms are carried out at the Center. The local public health authorities are responsible for the organization and administration of the mass surveys.

The findings are reported to the relevant central dispensaries, to which are also forwarded all film rolls and examination cards. The central dispensaries then conduct the follow-ups of detected positive cases and take any measures required, as for instance referring of the patients to sanatoria or hospitals. After the mass survey in a dispensary district, each central dispensary submits a statistical report to the Center. This report embraces the results of examinations of the follow-up cases, together with a classification of diagnoses on the pattern shown in table 3, which also summarizes the results of mass surveys carried out by the Center between 1946 and 1956.

Table 3. Result of mass chest examinations in Sweden carried out by the Mass Radiography Center of the Royal Medical Board during 1946–1956. (After S. Wijkström)

Number of persons examined	Attendance in %	Number of follow-up cases	% of number examined	Number of newly detected cases of pulmonary tuberculosis	‰ of number examined	Number of follow-up cases (non-tuberculous)	‰ of number examined
4,652,101	89.4	197,823	4.25	9,363	2.01	22,837	4.91

Photofluorographic Technique

Photofluorographic Apparatus, Film and Development

The fluorographic material was photographed by the technical staff of the Center under field conditions and with no modification of technical factors for test purposes.

All photofluorographic apparatuses were of Schönander make, type FFS-4 (half-wave apparatus).

Tubes: Machlett, with fixed anode; focus 2 × 2 mm; 15 kW.
Focus-screen distance 70 cm.
Grid of Schönander make. Ratio 8 : 1. 50 Lines per inch.
Screen: Patterson B 2.
Mirror optic with calculated aperture of *f*/0.68.
Camera: Schmidt Helm.
Resolving power: 4 lines per millimeter.
Exposure: 85 kW (30 mA constant).
Exposure times for antero-posterior projections: 0.25–0.7 sec.
» » » lateral » 0.5 –1.1 »
(Exposure times were governed by a phototimer.)
The photofluorograms were taken on Gaevert "Scopix" perforated roll film, 70 by 70 mm; size of image, 63 by 63 mm. Processing was done with Gaevert G 230 developer, and GP 230 was used as replenisher.
Duration of development 9 minutes; temperature 18°C.

Positioning in Photofluorography

In principle, each subject is photographed once while standing erect in the conventional antero-posterior position. Occasionally several exposures have to be made. Since 1955, moreover, lateral projections have been increasingly used, and are nowadays routine. For lateral projections the subject is positioned with the left side towards the screen.

Examination Cards

Each person to be photofluorographed receives, before the examination, a card on which the name, sex, date of birth, etc. are filled in. Further particulars are taken down concerning any history of pulmonary and/or cardiac disease, and any previous photofluorographic or roentgenographic examinations.

On the front of each examination card at the top are stamped the mobile unit's designation, the serial examination number and the date of examination.

These marks on the card are photographed together with the subject's chest. The final photofluorogram accordingly bears the same identification marks as the corresponding card, thus eliminating any possibility of subsequent confusion.

The examination cards are initially numbered in the same order as the corresponding photofluorograms, and are then sorted in batches. Each batch of cards matches a film roll containing a certain number of fluorograms.

This sequence is not broken until the photofluorograms are read, when the positive findings are picked out. Thereafter, the cards are sorted with respect to sex. Lastly, they are filed at the central dispensaries according to age groups and diagnoses, while the film rolls are stored in the order of their serial numbers.

If a subject's card is required at any time after the photofluorographic examination, it is looked up in the files with the aid of the name and date of birth. Its identification marks then enable the film roll with the subject's photofluorogram to be found. Conversely, an examination card can be found by means of the identification marks on the corresponding photofluorogram.

Reading of Photofluorograms

Principles of Photofluorogram Reading

A staff of nine or ten photofluorogram interpreters work at the Center. Five of them are full-time, the others part-time workers. They each have a separate room for reading, which can be darkened in daytime.

The full-time physicians have a working day of 5–6 hours; their part-time colleagues 2½–3 hours. The number of photofluorograms read daily by the full-time interpreters varies between 600 and 700; the other interpreters read about half that number.

The apparatus employed for reading the photofluorograms is of Schönander–Elema make, "Nelson" type, giving an enlargement of about 1.5 diameters.

Each interpreter makes a brief report on his observations of the localization, extent and appearance of any lesions. These reports are dictated on tape, then typed on the back of the relevant card. At the same time the interpreter himself annotates his evaluation of the need of follow-up examination.

The task of a photofluorogram interpreter is not only to detect all pathologic changes but to evaluate them with respect to their probable clinical significance and diagnosis. In addition he has to decide whether follow-up examination is required.

Photofluorographic findings can be broadly grouped as follows:

(1) No pathologic changes.

(2) Insignificant pathologic changes, as for instance calcified foci, minor pleural adhesions, etc.

(3) Significant or suspect pathologic changes requiring follow-up roentgen examination, observation or treatment ("follow-up cases").

It follows from the above classification that, as a general rule, only cases referable to group 3 are referred for follow-up examination and that the interpreter, in his evaluation of a finding, has the choice of only two alternatives.

Histories of tuberculosis or other pulmonary disease that are annotated on the examination card may sometimes, despite negative photofluorographic findings, prompt the interpreter to recommend follow-up examination.

It is of prime importance that all interpreters conform to the same norms in their evaluation of photofluorograms. However, different physicians studying a photofluorographic finding may form different opinions as to its clinical significance and the need of follow-up examination. In order that a new interpreter may adapt himself to the principles observed by his fellow readers, he receives directions and usually studies for some time the work of a few older and experienced interpreters. He is thus instructed in the precepts according to which he will subsequently have to read photofluorograms independently.

Dual Reading of Photofluorograms

Dual reading of all photofluorograms by two physicians was introduced in 1953. This method is designed to enhance the objectivity of interpretation, and hence the reliability of the photofluorographic diagnoses, with a view to eventual clinical evaluation of pathologic findings.

Economic and practical considerations, among others, lie behind the dual reading of known initial results. One physician accordingly does the initial reading of a photofluorogram series. He picks out all findings which in his opinion are pathologic or require follow-up examination, and annotates his evaluation of them on the relevant cards. The entire series is then re-read by a second physician, whose task is to check the first interpreter's results and correct them with regard to any overlooked or misinterpreted lesions; or otherwise to confirm the first reader's diagnoses. If the initial results require modification, the checking interpreter may consult either the first reader himself or one of the others. This checking procedure may yield some significant additional findings; and the two interpreters share the responsibility for the dual evaluation.

The two-man combinations for dual readings are continuously varied in

cycles. The work is so apportioned that the daily tasks of the interpreters are usually divided between initial reading and checking. In this way all interpreters team up by degrees with each of their colleagues, and grow familiar with each other's individual approach to the work.

The results of the initial and second readings, and the difference between them, were recorded, from 1953 to 1956, according to the following system.

Table 4. File card recording results after initial and second reading of photofluorograms.

Series no.: x–y Mobile unit: Z		Date of photography:	195
Initial reader: N Control reader: NN		Final results	
Initial result		Number of negative or insignificant findings	Number of significant findings (follow-up cases)
Number of negative or insignificant findings	395	393	2
Number of significant findings (follow-up cases)	20	1	19
Total	415	394	21

For each series of photofluorograms that had been read, a form was filled in with the serial numbers, identification of the mobile unit, and date of photofluorography. In addition the names of the initial and checking interpreters together with their results were annotated.

With this system it is fairly simple to observe the divergences between initial and second readings with respect to the correction of under- and over-diagnoses. This correction at the same time reflects the inter-individual difference emerging on dual reading. It envisages, however, only those photofluorographic diagnoses whose final clinical evaluation is unknown to both interpreters.

Under-diagnoses are calculated, as exemplified in table 3, according to the ratio of initially overlooked follow-up cases to the definitive number of follow-up cases; and are expressed in percent. For example: 2:21, corresponding to about 10 per cent.

Over-diagnoses are computed according to the ratio of over-diagnosed

cases to the initial number of follow-up cases, and are also expressed in percent. For example, 1 : 20, corresponding to 5 per cent.

Scrutiny of the records of a reader, acting either as initial or checking interpreter, enables the dual reading results to be calculated with respect both to the correction of his initial results by the other interpreters, and to his own critical appraisal of their initial results.

In accordance with these principles the effect was investigated of the above dual reading method in the general photofluorographic material evaluated by fourteen physicians during the period from 1953 to 1956.

II. Interpretation of the Test Material

Independent Individual Evaluations of the Test Material

The test material was evaluated in accordance with the precepts for the routine work. Eight physicians took part; six were full-time and two part-time interpreters. The first-named six read twenty test film rolls, totalling about 600 photofluorograms, per working day; the part-time readers, about one-half that number. The initial interpretation of the entire test material (i.e., 100 film rolls, containing 3,268 photofluorograms) thus occupied five working days for full-time physicians and ten for part-time ones. Before the investigation opened, the interpreters were instructed to evaluate the test material on the same principles as in an ordinary photofluorographic series. With each pathologic finding, they had to decide whether follow-up was necessary. In the evaluation of doubtful cases they had the possibility of consulting each other.

In evaluating the test material, the physicians did not have access to the aforementioned examination cards; for the particulars recorded thereon may influence an interpreter's results or arouse his attention, especially if they point to lung disease. On the other hand, he cannot rely upon their correctness, but is largely bound by his own evaluation of the photofluorographic findings, on which basis he has to make his diagnosis.

It is nevertheless evident that the absence of examination cards in this test investigation constituted a deviation from the normal working conditions, and to some extent handicapped the readers. For this reason only such test cases were selected in which the interpreters, at the original evaluation one to two years before the investigation, had not been influenced by data on the cards but had evaluated solely on the basis of the photofluorograms. Due to filing of the original cards at different places and in a different order, it was virtually impossible, however, to duplicate their original sequence.

Each interpreter first evaluated the entire test material alone. His observa-

tions of pathologic changes and his evaluation thereof were annotated on blank cards, on which the photofluorogram serial number was also recorded. The interpreter made out cards only for photofluorographic findings which, in his opinion, were worth recording or were judged to be follow-up cases.

These cards represented the initial results of each interpreter after his individual evaluation. They were collected at the end of each working day, and stored until all interpreters had completed their initial readings. There were no possibilities for an interpreter to modify his own initial results during the test.

Dual Reading of the Test Material

When all eight interpreters had completed their initial evaluations, dual reading of the test material opened, in accordance with the method applied at the Center, after intervals varying between one and two months. There was little likelihood of an interpreter remembering his own initial findings, having regard to the magnitude of the material and to the daily reading of routine photofluorograms parallel with the test series.

Originally the dual reading was so planned that each interpreter would check the initial results of each of his seven colleagues. Hence, his own initial results would have been checked seven times. Since all interpreters made initial evaluations of the test material there were, for each two-man team, two initial sets of results that could be checked. In a combination of interpreters A and B, either of the two could check the other's results. The two sets of final results thus obtained were not necessarily identical; they could be dependent on the efficiency of the checking interpreter and quality of the initial results.

Theoretically there were fifty-six possible two-man combinations of these eight as first and second interpreters. However, for practical reasons this program had to be so modified that each interpreter checked at least four sets of initial results; and conversely his own initial results were checked by at least four colleagues. During the investigation forty of the fifty-six possible combinations were realized. (Table 22.)

In dual reading, the checking interpreter received the test material together with the cards on which the first interpreter had annotated his findings and evaluations. The entire series had to be read as though under routine conditions, and the first interpreter's results corrected with respect to overlooked or misinterpreted pathologic findings. If the checking interpreter disagreed with a diagnosis, he made out a new card for that particular photofluorographic finding and recorded thereon the modification he would have made under routine conditions. These cards represented his own additional findings and corrections and, together with the first interpreter's findings, constituted

the final result after the dual reading. The cards were collected at the end of each working day and stored for analysis.

The interpreters had as much time for checking as for the initial reading. Thus a full-time physician checked the entire test material in five working days; a part-time colleague, in ten days. The one hundred film rolls were divided into five sets of twenty rolls each and distributed among the interpreters systematically, to ensure as far as possible an interval of at least one week before the same film series was returned to an interpreter for checking another set of initial results. The dual reading in forty combinations proceeded for about five months.

Collection of Data from the Test Material

In single reading of the test series each interpreter annotated his findings and their evaluation on blank cards, at the same time recording thereon the corresponding photofluorogram identification marks. From each reader was thus obtained a batch of cards which included those for the test cases he had observed; in addition there were a number of cards relating to evaluation of pulmonary findings in the rest of the material. The cards were then sorted and those for test cases picked out; this revealed the number and identity of test cases noted by each reader, as well as the number of them that he had regarded as follow-up cases.

For each test photofluorogram a card was made out on which the various interpreters' evaluations were entered, using special identifying marks. The different readers were then paired in all possible combinations of pseudoteams, whose results could then be compared with the corresponding results of forty dual readings of known initial results. The pseudoteams' scores were composed of a number of test cases evaluated identically by both interpreters and a number of photofluorographic findings that one reader alone had detected or regarded as follow-up cases.

The cards for the other positive findings in the remaining test material were subjected to a similar procedure. This provided an indication of how the various findings in the material had been evaluated by the different readers.

When single reading of the test material had been completed and the interpreters' personal results calculated, the checking of known results began. Here the second readers had the batches of cards with the first readers' results. On detecting a positive finding overlooked by the first interpreter, they annotated their observations and evaluation on a fresh card bearing the identification marks of the respective two-man combination. These additional findings were subsequently picked out, and in this way it was possible to calculate

the number of test findings detected by the second reader showing the number of positive cases he added to the initial reader's results. This was performed for the test photofluorograms and the remaining test material separately. Using this method, the results of the different two-man combinations were then compared.

Factors Influencing the Interpretation of Photofluorograms

In the interpretation of photofluorograms, the reliability of the results depends just as much on technical conditions as on the efficiency of the reading itself. Everyone who is cognizant with the evaluation of photofluorograms from mass chest examinations will thus appreciate the advances that have been made in recent years, with the elaboration and improvement of roentgenologic and photographic equipment. The chief aim here has been to ensure a consistently high quality of photofluorographic images that will be conducive to adequate diagnosis.

Technique

The quality of a photofluorographic image produced by the roentgen apparatus depends upon electrical and optical factors, among others. Since the exposure time as well as the density and contrast of the processed film are in turn dependent upon the power supply, the electrical resources available under field conditions have a very important bearing on the production of satisfactory images. If gasoline generators are used, they must be able to maintain a constant voltage throughout the exposure, so as to ensure satisfactory contrast.

The resolving power of the camera's optical system is a significant factor relative to definition of the image. The latter's quality may also be influenced by other technical factors including the lens aperture, quality of the screen and antidiffusion effect of the grid, and the focus-screen distance.

The use of photofluorographic apparatus calls for skilled personnel, who must be able not only to operate their machines efficiently, but also to detect both mechanical flaws and failures in the power supply. Their perspicacity and responsibility may enable a great deal of diagnostic errors to be avoided. Similar considerations apply to the processing of survey films by the photographic staff.

The subject examined constitutes yet another factor that may influence the quality of the image. Obesity, thoracic deformities, motor restlessness in children, and mental deficiency often handicap the production of satisfactory photofluorograms.

Due to the varying sizes of photofluorograms and the variability of interpretative criteria with different dimensions of roentgen films, the reader must possess some degree of adaptability. A pulmonary lesion on a photofluorogram may, by virtue of the latter's lower resolving power, be more distinct and homogeneous but less detailed than its counterpart on a 14 by 17 inch roentgenogram. If a reader expects, on a photofluorogram, such definition of details that is possible only on the larger film, he may well overlook minor pulmonary lesions or misinterprete their clinical significance. Since the appearance of any particular tuberculous lesion may vary with the size of the film while its clinical significance is the same, the reader must, for adequate interpretation, apply different criteria according to the film dimensions. This requires some training and experience before he can be sufficiently familiar with the diagnostic criteria of the photofluorographic method; without this, his interpretation of survey films will be subject to numerous errors.

Observer Errors

The yield of newly detected cases in mass chest examinations is largely dependent on the type of population examined, as well as the adequate interpretation of observed lesions and, not least, the clinical investigation of suspected pathologic findings. In the evaluation of serial photofluorograms from mass surveys, the cardinal aim is to detect as many new cases as possible while seeking to avoid unnecessary follow-up examinations. An ideal solution of this problem is scarcely feasible, for if the number of overlooked cases can be reduced at all, it is usually at the expense of an increased over-diagnosis rate; and vice versa. Hence the photofluorogram interpreter has to compromise and strike some sort of balance between these two desiderata. None the less, the main emphasis must be on detection of the greatest possible number of cases, which in turn helps to protect the health and lives of the population examined.

Efficient reading presupposes not only the observation of pathologic conditions but evaluation of their clinical significance. Some of the causes behind low rates of observation and identification of pathologic changes are physical factors such as poor visual acuity, and psychologic ones such as mental fatigue or boredom with the monotony of routine work. Insufficient training and experience may be responsible for inadequate interpretation of lesions even though these are correctly identified. A reader's efficiency accordingly depends upon his alertness and accuracy as well as his competence.

The qualities of photofluorogram interpreters naturally vary with their types of personality, their qualifications, experience and training. This inescapable fact not only explains the undesirable inter-individual variations

associated with interpretation of survey films; it is also one of the main sources of the human error. YERUSHALMY and his co-workers, as mentioned in the foregoing, have already conducted several investigations into the causes of the individual observer error. The purpose of the present study is to elucidate the significance of this error in the evaluation of mass photofluorograms, with reference to various multiple reading methods, in the hope of reducing its effect to the minimum.

CHAPTER III

Results

All Readers' Results after Dual Evaluation of the General Photofluorographic Material from Mass Surveys in Sweden, 1953–1956

In the following are reported the initial reading results and the amendments thereof on checking of the photofluorographic material from mass chest examinations in Sweden during the period from 1953 to 1956. The photofluorograms were read twice by 14 physicians according to the aforementioned method applied at the Center. The amendments were of initial under- or over-diagnoses, and are recorded both in absolute figures and percentages. The under-diagnosis rate was calculated from the ratio of follow-up cases detected at second reading to the final number of follow-up cases; the over-diagnosis rate from the ratio of initially over-diagnosed cases to the original number of follow-up cases. During the initial and second reading the physicians evaluated varying numbers of photofluorograms, depending on their hours of work and duration of employment at the Center. The results of second reading in relation to each physician's initial results are detailed in table 5.

This table provides a survey of 2,084,583 photofluorographic diagnoses after initial reading and checking. On first reading of this series, 59,708 follow-up cases were detected, representing 2.9 per cent of the population examined. Following second reading the number rose to 63,852, or 3.1 per cent of the relevant population; at the same time 1,128 of the original 59,708 were evaluated as either insignificant or negative. On subtraction of the over-diagnosed cases from the difference between the final and initial number of follow-up cases, it was found that 5,272 positive photofluorographic findings, or 8.3 per cent of the definitive 63,852 follow-up cases, had not been detected until the second reading.

Results after Initial Reading

In the different series initially read by the individual interpreters, the incidence of follow-up cases varied between 1.3 and 3.7 per cent of the photofluorograms evaluated. After calculation of statistical errors in the percentual

Table 5. Summary of the individual results after initial interpretation of photofluorograms with special reference to the correction of diagnoses by dual reading. Estimation of errors according to formula: Error of percentage (P) = $= \pm \sqrt{[p(100 - p)]}/\sqrt{n}$. n = total number of cases.

Reader	I Number of photofluorograms	II Number of "positive" photofluorograms after initial reading	% of I	III Number of "positive" photofluorograms after dual reading	% of I	IV Number of missed positive findings in initial reading	% of III	V Number of "overdiagnosed" findings in initial reading	% of II
1	137,736	1,847	1.3 ± 0.03	2,528	1.8 ± 0.04	704	27.8 ± 0.9	23	1.2 ± 0.26
2	3,009	100	3.3 ± 0.33	117	3.9 ± 0.35	17	14.5 ± 3.3	0	0.0 ± 0.99
3	313,645	7,752	2.5 ± 0.03	8,821	2.8 ± 0.03	1,186	13.4 ± 0.4	117	1.5 ± 0.14
4	289,902	7,003	2.4 ± 0.03	7,904	2.7 ± 0.03	971	12.3 ± 0.4	70	1.0 ± 0.12
5	41,074	1,537	3.7 ± 0.09	1,626	4.0 ± 0.10	180	11.1 ± 0.8	91	5.9 ± 0.60
6	7,490	266	3.6 ± 0.22	287	3.8 ± 0.22	31	10.8 ± 1.8	10	3.8 ± 1.17
7	16,680	487	2.9 ± 0.13	531	3.2 ± 0.14	55	10.3 ± 1.3	11	2.3 ± 0.67
8	306,944	10,768	3.5 ± 0.03	11,390	3.7 ± 0.03	947	8.3 ± 0.3	325	3.0 ± 0.17
9	231,848	5.402	2.3 ± 0.03	5,734	2.5 ± 0.03	345	6.0 ± 0.3	13	0.2 ± 0.07
10	17,251	562	3.3 ± 0.14	530	3.1 ± 0.13	29	5.5 ± 1.0	61	10.9 ± 1.31
11	159,488	4,962	3.1 ± 0.04	5,074	3.2 ± 0.04	232	4.6 ± 0.3	120	2.4 ± 0.22
12	6,380	217	3.4 ± 0.23	224	3.5 ± 0.23	10	4.5 ± 1.4	3	1.4 ± 0.79
13	306,293	10,359	3.4 ± 0.03	10,427	3.4 ± 0.03	318	3.0 ± 0.2	250	2.4 ± 0.15
14	246,843	8,446	3.4 ± 0.04	8,659	3.5 ± 0.04	247	2.9 ± 0.2	34	0.4 ± 0.07
Total	2,084,583	59,708	2.9	63,852	3.1	5,272	8.3	1,128	1.9

figures, it was quite evident that this variation could not have been due to chance. It might otherwise have been attributable to variable sources of the initial series, i.e., population groups with varying pulmonary disease morbidity rates. However, the material as a whole was so apportioned that the interpreters each had mixed series from mass surveys throughout the country. Similar inter-individual differences emerged after correction of the readers' initial results, and showed almost the same statistical significance. Despite checking of each reader's initial results, usually by the majority of his colleagues, the discrepancies between first readers were still evident in the final percentages of follow-up cases. This may have been due to a possible difference between interpreters acting as second readers.

Correction of Each Initial Reader's Under- and Overdiagnoses on Second Reading

The photofluorographic findings that were initially overlooked or underestimated by different readers amounted to between 2.9 and 27.8 per cent of the final positive findings after the dual reading. The interpreters' results in table 5 were graded according to the percentual correction of under-diagnoses; this was considered to be, in practice, of the greatest importance for judging the efficiency of dual reading. Analysis of the under-diagnosis rates once more showed a significant statistical difference between several of the readers.

On dual reading of the total material, 1,128 or 1.9 per cent of the 59,708 initial follow-up cases were evaluated as negative or insignificant findings. As regards the individual results, correction of over-diagnoses varied from 0.0 to 10.9 per cent of the initial follow-up cases. Here, too, substantial differences accordingly emerged and they were often statistically significant.

An exceptionally noteworthy finding was the absence of any observable correlation between the initial readers' figures for over-diagnoses and under-diagnoses (table 5, colums IV and V).—This suggests, in principle, a fundamental difference between the interpreters in their approach to the photofluorogram: from the reader who, probably, accepts only distinct pulmonary lesions (high under-diagnoses—low over-diagnoses) to the subtle reader (low under-diagnoses—high over-diagnoses); but also from the confident (low under-diagnoses—low over-diagnoses) to the unconfident (high under-diagnoses—high over-diagnoses) observer.

Each Reader's Personal Correction of Initial Under- and Over-diagnoses on Second Reading

Following this discussion of the initial reading results and their errors in

the light of the second reading, the interpreters will now be studied in their capacity of second readers.

All physicians with the exception of reader no. 12 did second readings, the results of which are detailed in table 6. In column I are shown the total numbers of photofluorograms checked by each reader irrespective of who had done the initial reading. This enables an idea to be gained of the interpreters' relative efficiency as second readers. The series checked were not uniformly apportioned, quantitatively, among the readers. The incidence of initial follow-up cases varied from 2.1 to 3.2 per cent of the respective series (column II). Each reader's series was composed of initial results referable to most of his colleagues. The second reading results disclosed substantial differences between the readers in their personal corrections. While one reader detected 0.0 per cent follow-up cases that had initially been overlooked, another might find 12.6 per cent in his material. The differences in correction of "over-diagnosed" cases were substantial, ranging from 0.0 to 6.7 per cent of the initial follow-up cases.

The statistical errors were also calculated for the results of these second readings, significant percentual differences emerging between different interpreters. Here, however, the discrepancies may conceivably have been due to varying proportions, in the second readers' series, of photofluorograms from different initial readers. Such discrepancies should have been equalized to some extent, the dual reading having been so arranged as to ensure most of the possible combinations of first and second readers. That they were not fully equalized is evident, however, from the fact that the percentages in table 6, column II, still differ in some cases, though not so much as the corresponding values in table 5, column II. The corrections of over- and under-diagnoses in table 6, columns IV and V, nevertheless show statistically significant differences between several readers, even though the incidences of initial follow-up cases in their respective series varied only to a minor degree. This suggests that the interpreters also differed in their capacity of second readers and not merely when acting as initial readers.

Nor is there here any significant correlation between corrections of over- and under-diagnoses in table 6, columns IV and V. The readers' efficiency grades should thus be evident here too, as in initial reading. And indeed, comparison of the values in columns IV of tables 5 and 6 shows a distinct inverse relationship; i.e., a reader with a high initial under-diagnosis rate corrected fewer of his colleagues' under-diagnoses. A similar inverse relationship for over-diagnoses can be observed on comparison of columns V in tables 5 and 6. An interpreter with a high personal rate of initial over-diagnoses also accepted the probable over-diagnoses of the other readers, while one with a low personal rate corrected their probable over-diagnoses to a large extent.

Table 6. Summary of the individual results after second reading of photofluorograms with special respect to the correction of initial diagnoses. Estimation of errors according to formula: Error of percentage (P) = $= \pm \sqrt{[p(100-p)]}/\sqrt{n}$. n = total number of cases.

Reader	I Number of photofluorographic diagnoses checked	II Number of "positive" photofluorograms according to initial reading	% of I	III Number of "positive" photofluorograms after second reading	% of I	IV Number of additional pos. findings findings missed in second reading	% of III	V Number of "negative" findings overdiagnosed in initial reading	% of II
1	105,378	2,447	2.3 ± 0.05	2,342	2.2 ± 0.05	18	0.8 ± 0.18	123	5.0 ± 0.44
2	374	10	2.7 ± 0.83	10	2.7 ± 0.83	0	0.0 ± 9.49	0	0.0 ± 9.49
3	286,043	8,267	2.9 ± 0.03	8,782	3.1 ± 0.03	549	6.3 ± 0.26	34	0.4 ± 0.07
4	196,817	6,012	3.1 ± 0.04	6,199	3.1 ± 0.04	222	3.6 ± 0.24	35	0.6 ± 0.10
5	76,230	2,314	3.0 ± 0.06	2,529	3.3 ± 0.06	236	9.3 ± 0.58	21	0.9 ± 0.20
6	10,180	234	2.3 ± 0.15	249	2.4 ± 0.15	16	6.4 ± 1.55	1	0.4 ± 0.42
7	13,523	388	2.9 ± 0.14	409	3.0 ± 0.15	40	9.8 ± 1.47	19	4.9 ± 1.10
8	290,330	8,449	2.9 ± 0.03	9,192	3.2 ± 0.03	778	8.5 ± 0.29	35	0.4 ± 0.07
9	312,347	8,279	2.7 ± 0.03	8,481	2.7 ± 0.03	493	5.8 ± 0.25	291	3.5 ± 0.20
10	15,810	335	2.1 ± 0.11	381	2.4 ± 0.12	48	12.6 ± 1.70	2	0.6 ± 0.42
11	190,792	5,195	2.7 ± 0.04	5,812	3.0 ± 0.04	668	11.5 ± 0.42	51	1.0 ± 0.14
12	—	—	—	—	—	—	—	—	—
13	412,421	12,132	2.9 ± 0.03	13,583	3.3 ± 0.03	1,591	11.7 ± 0.28	140	1.2 ± 0.10
14	174,338	5,646	3.2 ± 0.04	5,883	3.4 ± 0.04	613	10.4 ± 0.40	376	6.7 ± 0.33
Total	2,084,583	59,708	2.9	63,852	3.1	5,272	8.3	1,128	1.9

Reciprocal Checking by Different Two-Man Combinations

The dual reading was carried out with known initial results. In some combinations of pairs this might conceivably have influenced the critical approach of the second reader to the initial results. The dual reading results of the various pairs were accordingly subjected to a comparative study designed to ascertain if a reader's initial results were evaluated uniformly by all of the others, and to elucidate his personal score when checking their initial results.

The results of the correction of *initial under-diagnoses* are given in table 7. Some combinations are lacking because the respective periods of employment at the Center did not coincide. The second-reading results in relation to each interpreter's initial findings as checked by his colleagues are listed horizontally in the table; each reader's personal corrections of his colleagues' initial results, vertically. The amendments are expressed as the ratios of the second reader's additional findings to the final number of positive findings. The results are condensed in the margins and correspond to columns IV of tables 5 and 6.

Just as the majority of interpreters exhibited substantial differences in their initial evaluations, so did they vary, as shown by table 7, when checking each other's initial findings; for these were amended to varying extents. It emerged that readers who themselves, as shown in table 5, column IV, had high under-diagnosis rates did not, as a rule, find many initially misdiagnosed cases when they checked their colleagues' results. If the readers were graded with respect to their findings, the percentages of follow-up cases added to their initial results by the second interpreters tended to be higher or lower according to their grading. The tabulation suggests that the grades based on initial under-diagnoses were retained, on the whole, when the first readers did checking and also when their personal findings were checked. Personal corrections of initial under-diagnoses amounted to between 0.0 and 12.6 per cent of the final number of follow-up cases in the respective series of checked photofluorograms. Yet when some readers' initial results were checked by their colleagues, their initial under-diagnoses could amount to as much as 38.4 per cent of all follow-up cases detected in their particular series. In some combinations of pairs, however, there was no concordance with the reader's grade in the table; i.e., an interpreter with a high personal under-diagnosis rate might find a greater percentage of missed diagnoses on checking another reader whose under-diagnoses, according to the other interpreters' evaluations, were considerably fewer than his own; and vice versa. Comparison with table 5 indicates that interpreters with high initial over-diagnosis rates usually corrected under-diagnoses more often than did those with relatively low corresponding rates.

Table 7. Reciprocal correction, by pairs of interpreters, of initial under-diagnoses on

Horizontally: Correction of under-diagnoses on second reading of initial reader's res

Reader	*1*	*2*	*3*	*4*	*5*	*6*	*7*
1			44 258 17.1 %	20 142 14.1 %			
2			4 51 7.8 %	6 17 35.3 %			
3	3 228 1.3 %			87 1,347 6.5 %	106 826 12.8 %	2 27 7.4 %	19 174 10.9 %
4	2 255 0.8 %		108 1,054 10.2 %		31 393 7.9 %	3 12 25.0 %	7 96 7.3 %
5	4 53 7.5 %		28 308 9.1 %	14 183 7.7 %			
6			4 83 4.8 %	2 24 8.3 %			
7			7 111 6.3 %	6 64 9.4 %			
8	5 330 1.5 %	0 8 —	101 1,701 5.9 %	38 1,056 3.6 %	53 534 9.9 %	9 82 11.0 %	
9	0 158 0.0 %	0 2 —	62 1,272 4.9 %	9 620 1.5 %	16 184 8.6 %	1 36 2.8 %	8 58 13.8 %
10	0 5 —		3 27 11.1 %				
11	2 407 0.5 %		39 628 6.2 %	8 330 2.4 %	4 83 4.8 %	0 7 —	
12	0 13 0.0 %		2 12 16.7 %				
13	1 312 0.3 %		100 2,159 4.6 %	15 1,394 1.1 %	20 351 5.7 %	1 79 1.3 %	5 71 7.0 %
14	1 581 0.2 %		40 1,118 3.6 %	17 1,022 1.7 %	6 158 3.8 %	0 6 —	1 10 10.0 %
Total	18 2,342 0.8 %	0 10 0.0 %	549 8,782 6.3 %	222 6,199 3.6 %	236 2,529 9.3 %	16 249 6.4 %	40 409 9.8 %

eading of the general photofluorographic material from 1953–1956. *See text, page 37.*

ertically: Second reader's correction of initial under-diagnoses.

8	9	10	11	12	13	14	Total
158 / 458 / 34.5 %	76 / 460 / 16.5 %	14 / 41 / 34.1 %	150 / 391 / 38.4 %		185 / 557 / 33.2 %	57 / 221 / 25.8 %	704 / 2,528 / 27.8 %
3 / 11 / 27.3 %					4 / 25 / 16.0 %	0 / 13 / 0.0 %	17 / 117 / 14.5 %
228 / 1,083 / 21.1 %	170 / 2,051 / 8.3 %	5 / 56 / 8.9 %	229 / 1,186 / 19.3 %		237 / 1,315 / 18.0 %	100 / 528 / 18.9 %	1,186 / 8,821 / 13.4 %
137 / 1,738 / 7.9 %	70 / 907 / 7.7 %	13 / 85 / 15.3 %	105 / 579 / 18.1 %		373 / 2,084 / 17.9 %	122 / 701 / 17.4 %	971 / 7,904 / 12.3 %
20 / 320 / 6.3 %	22 / 169 / 13.0 %		27 / 185 / 14.6 %		34 / 181 / 18.8 %	31 / 227 / 13.7 %	180 / 1,626 / 11.1 %
			4 / 14 / 28.6 %		21 / 166 / 12.7 %		31 / 287 / 10.8 %
15 / 71 / 21.1 %	5 / 111 / 4.5 %				15 / 111 / 13.5 %	7 / 63 / 11.1 %	55 / 531 / 10.3 %
	67 / 1,332 / 5.0 %	8 / 27 / 29.6 %	90 / 1,197 / 7.5 %		437 / 3,926 / 11.1 %	139 / 1,197 / 11.6 %	947 / 11,390 / 8.3 %
56 / 965 / 5.8 %		0 / 12 / 0.0 %	19 / 315 / 6.0 %		115 / 1,313 / 8.8 %	59 / 799 / 7.4 %	345 / 5,734 / 6.0 %
0 / 1 / —	1 / 32 / 3.1 %		2 / 26 / 7.7 %		1 / 57 / 1.8 %	22 / 382 / 5.8 %	29 / 530 / 5.5 %
51 / 812 / 6.3 %	11 / 487 / 2.3 %	1 / 37 / 2.7 %			89 / 1,810 / 4.7 %	27 / 473 / 5.7 %	232 / 5,074 / 4.6 %
	5 / 92 / 5.4 %		0 / 27 / 0.0 %		3 / 79 / 3.8 %	0 / 1 / —	10 / 224 / 4.5 %
64 / 2,121 / 3.0 %	26 / 1,444 / 1.8 %	7 / 56 / 12.5 %	30 / 1,162 / 2.6 %			49 / 1,278 / 3.8 %	318 / 10,427 / 3.0 %
46 / 1,612 / 2.9 %	40 / 1,396 / 2.9 %	0 / 67 / 0.0 %	12 / 730 / 1.6 %		77 / 1,959 / 3.9 %		247 / 8,659 / 2.9 %
778 / 9,192 / 8.5 %	493 / 8,481 / 5,8 %	48 / 381 / 12.6 %	668 / 5,812 / 12.4 %		1,591 / 13,583 / 11.7 %	613 / 5,883 / 10.4 %	5,272 / 63,852 / 8.3 %

Table 8. Reciprocal correction, by pairs of interpreters, of initial over-diagnoses on

Horizontally: Correction of over-diagnoses on second reading of initial reader's re

Reader	1	2	3	4	5	6	[illegible]
1			0/214 0.0 %	0/122 0.0 %			
2			0/47 0.0 %	0/11 0.0 %			
3	4/229 1.7 %			0/1,260 0.0 %	4/724 0.6 %	0/25 0.0 %	2/15[illegible] 1.3 %
4	5/258 1.9 %		8/954 0.8 %		1/363 0.3 %	0/9 —	1[illegible]/9[illegible] 10.1 %
5	9/58 15.5 %		7/287 2.4 %	7/176 4.0 %			
6			0/79 0.0 %	1/23 4.3 %			
7			0/104 0.0 %	0/58 0.0 %			
8	36/361 10.0 %	0/8 —	10/1,610 0.6 %	12/1,030 1.2 %	11/492 2.2 %	1/74 1.4 %	
9	0/158 0.0 %	0/2 —	4/1,214 0.3 %	0/611 0.0 %	2/170 1.2 %	0/35 0.0 %	0/50 0.0 %
10	3/8 —		0/24 0.0 %				
11	17/422 4.0 %		1/590 0.2 %	10/332 3.0 %	0/79 0.0 %	0/7 —	
12	0/13 0.0 %		0/10 0.0 %				
13	46/357 12.9 %		3/2,062 0.1 %	4/1,383 0.3 %	3/334 0.9 %	0/78 0.0 %	7/73 9.6 %
14	3/583 0.5 %		1/1,072 0.1 %	1/1,006 0.1 %	0/152 0.0 %	0/6 —	0/9 —
Total	123/2,447 5.0 %	0/10 0.0 %	34/8,267 0.4 %	35/6,012 0.6 %	21/2,314 0.9 %	1/234 0.4 %	19/388 4.9 %

ading of the general photofluorographic material from 1953–1956. See text, page 42.

ertically: Second reader's correction of initial over-diagnoses.

	8	9	10	11	12	13	14	Total
	7/307 2.3 %	11/395 2.8 %	0/27 0.0 %	2/243 0.8 %		2/374 0.5 %	1/165 0.6 %	23/1,847 1.2 %
	0/8 —					0/21 0.0 %	0/13 0.0 %	0/100 0.0 %
	7/862 0.8 %	67/1,948 3.4 %	0/51 0.0 %	5/962 0.5 %		3/1,081 0.3 %	25/453 5.5 %	117/7,752 1.5 %
	4/1,605 0.2 %	13/850 1.5 %	0/72 0.0 %	0/474 0.0 %		15/1,726 0.9 %	14/593 2.3 %	70/7,003 1.0 %
	1/301 0.3 %	16/163 9.8 %		8/166 4.8 %		14/161 8.7 %	29/225 12.9 %	91/1,537 5.9 %
				0/10 0.0 %		9/154 5.8 %		10/266 3.8 %
	0/56 0.0 %	7/113 6.2 %				1/97 1.0 %	3/59 5.1 %	11/487 2.3 %
		78/1,343 5.8 %	0/19 0.0 %	22/1,129 1.9 %		48/3,537 1.3 %	107/1,165 9.2 %	325/10,768 3.0 %
	2/911 0.2 %		0/12 0.0 %	0/296 0.0 %		0/1,198 0.0 %	5/745 0.7 %	13/5,402 0.2 %
	0/1 —	0/31 0.0 %		0/24 0.0 %		1/57 1.8 %	57/417 13.7 %	61/562 10.9 %
	2/763 0.3 %	21/497 4.2 %	0/36 0.0 %			45/1,766 2.5 %	24/470 5.1 %	120/4,962 2.4 %
		0/87 0.0 %		0/27 0.0 %		0/76 0.0 %	3/4 —	3/217 1.4 %
	9/2,066 0.4 %	54/1,472 3.7 %	2/51 3.9 %	14/1,146 1.2 %			108/1,337 8.1 %	250/10,359 2.4 %
	3/1,569 0.2 %	24/1,380 1.7 %	0/67 0.0 %	0/718 0.0 %		2/1,884 0.1 %		34/8,446 0.4 %
	35/8,449 0.4 %	291/8,279 3.5 %	2/335 0.6 %	51/5,195 1.0 %		140/12,132 1.2 %	376/5,646 6.7 %	1,128/59,708 1.9 %

Table 8 shows the interpreters' reciprocal corrections of *initial over-diagnoses*. The ratios of initially over-diagnosed findings to initial follow-up cases are given for each pair of readers. Corrections of a reader's initial results are listed horizontally, and each interpreter's personal amendments vertically, in the table. The results are condensed in the margins and correspond to columns V in tables 5 and 6.

In general, over-diagnoses were corrected to a much lesser extent. In the initial results of the different readers, however, over-diagnoses varied between 0.0 and 10.9 per cent of the initial follow-up cases. The interpreters' personal corrections comprised between 0.0 and 6.7 per cent of the initial follow-up cases. The table reveals a marked variability in the scores of different second readers when checking the initial evaluations of another interpreter. Yet some correlation is detectable between readers with low personal over-diagnosis rates, who more often corrected others with high corresponding rates, and those with high personal over-diagnosis rates, who modified the others' over-diagnoses on a smaller scale. Conversely, there were some combinations of pairs in which an interpreter with a low over-diagnosis rate modified fewer over-diagnoses of a colleague who, according to most of the other second readers, probably had a high over-diagnosis rate. Here, too, a conspicuous variability was thus found in the re-evaluations of possibly over-diagnosed initial findings.

Amendment of a photofluorographic finding that has been classed as a follow-up case implies the acceptance of some responsibility which the second reader may often be reluctant to assume. It is not clear, however, whether the marked variability in corrections of over-diagnoses was chiefly due to this psychologic factor or to genuinely different evaluations of photofluorograms.

Test Readers' Results after Dual Evaluation of the General Photofluorographic Material from Mass Surveys in Sweden, 1953–1956

Since the eight test interpreters had also evaluated the general material, they have been extracted from tables 7 and 8 and the results of their reciprocal checking are listed in tables 9 and 10. They can be identified from the preceding codification.

These eight readers had evaluated a total of 1,501,810 photofluorograms—i.e., three-fourths of the general material—during the course of initial and second reading. The results of the reciprocal correction, with respect to initially under-diagnosed cases, are set forth in table 9 on the same pattern as above. In principle, the same differences emerged between the initial results

and those obtained when the latter were checked or when the first readers themselves acted as checkers. As regards the *correction of under-diagnoses* by the other interpreters, there was a distinct rising tendency; i.e., the percentages of additional follow-up cases increased with the mounting grade of the second reader. Conversely, the corresponding percentages referable to second readers tended to fall with ascending grade of the initial interpreter. Altogether, 3,872 or 8.8 per cent of the final 43,806 follow-up cases were detected at re-evaluation. The personal under-diagnosis rates of the test readers varied from 2.8 to 28.0 per cent of the final number of follow-up cases in their initial results. When the readers themselves checked each other's initial test results, they found between 0.8 and 13.0 per cent of follow-up cases in their series.

The interpreters' grading on second evaluation of *initial over-diagnoses* was similar to that evident in tables 7 and 8. The results in this respect are shown in table 10. Interpreters with low personal over-diagnosis rates thus showed a greater tendency to correct their colleagues' initial over-diagnoses; and vice versa. Over-diagnoses in the individual initial results were corrected to the extent of 0.1–2.8 per cent of the initial follow-up cases in the relevant series, whereas the interpreters personally modified between 0.4 and 6.2 per cent of the initial positive findings in the series allocated to them for second reading.

Summary of Results after Dual Reading of the General Photofluorographic Material

On re-evaluation of the general material by fourteen interpreters, 5,272 or 8.3 per cent of the final number of follow-up cases were detected. As regards the individual initial results, a significant difference emerged between some readers. The individual under-diagnosis rate at first reading ranged from 2.9 to 27.8 per cent of the final numbers of follow-up cases. The discrepancies between readers were evident not only in their own initial evaluations of photofluorograms, but also in their checking of one another's results. The differences were statistically significant.

At second reading, 1,128 or 1.9 per cent of the initial follow-up cases were considered to be over-diagnosed findings. The readers' individual over-diagnosis rates in the initial results varied between 0.0 and 10.9 per cent of the initial follow-up cases; here, too, statistically significant differences were found between the interpreters. These differences were also evident when the readers themselves checked each other's over-diagnoses. The same variability was found on analysis of the test readers' initial results and on reciprocal checking of them.

Table 9. Reciprocal correction, by pairs of test readers, of initial under-diagnoses on dual reading of the general photofluorographic material from 1953–1956. See text, page 42.

Horizontally: Correction of under diagnoses on second reading of initial reader's results.
Vertically: Second reader's correction of initial under-diagnoses.

Reader	1	3	4	8	9	10	11	13	Correction of under-diagnoses on second reading of initial reader's results and number of photofluorograms checked
1		44/258 17.1 %	20/142 14.1 %	158/458 34.5 %	76/460 16.5 %	14/41 34.1 %	150/391 38.4 %	185/557 33.2 %	647/2,307 28.0 % 125,760
3	3/228 1.3 %		87/1,347 6.5 %	228/1,083 21.0 %	170/2,051 8.3 %	5/56 8.9 %	229/1,186 19.3 %	237/1,315 18.0 %	959/7,266 13.2 % 265,978
4	2/255 0.8 %	108/1,054 10.2 %		137/1,738 7.9 %	70/907 7.7 %	13/85 15.3 %	105/579 18.1 %	373/2,084 13.1 %	808/6,702 12.1 % 248,616
8	5/330 1.5 %	101/1,701 5.9 %	38/1,056 3.6 %		67/1,332 5.0 %	8/27 29.6 %	90/1,197 7.5 %	437/3,926 11.1 %	746/9,569 7.8 % 258,554
9	0/158 0.0 %	62/1,272 4.9 %	9/620 1.4 %	56/965 5.8 %		0/12 0.0 %	19/315 6.0 %	115/1,313 8.8 %	261/4,655 5.6 % 196,690
10	0/5 —	3/27 11.1 %	0/0 —	0/1 —	1/32 3.1 %		2/26 7.7 %	1/57 1.8 %	7/148 4.7 % 7,008
11	2/407 0.5 %	39/628 6.2 %	8/330 2.4 %	51/812 6.3 %	11/487 2.3 %	1/37 2.7 %		89/1,810 4.9 %	201/4,511 4.5 % 143,241
13	1/312 0.3 %	100/2,159 4.6 %	15/1,394 1.1 %	64/2,121 3.0 %	26/1,444 1.8 %	7/56 12.5 %	30/1,162 2.6 %		243/8,648 2.8 % 255,963
Second reader's correction of initial under-diagnoses and number of photofluorograms checked	13/1,695 0.8 % 84,080	457/7,099 6.4 % 239,513	177/4,889 3.6 % 162,318	694/7,178 9.7 % 238,443	421/6,713 6.3 % 258,538	48/314 15.3 % 13.912	625/4,856 12.9 % 166,136	1,437/11,062 13.0 % 338,870	3,872/43,806 8.8 % 1,501,810

Table 10. Reciprocal correction, by pairs of test readers, of initial over-diagnoses on dual reading of the general photofluorographic material from 1953–1956. See text, page 43.

Horizontally: Correction of over-diagnoses on second reading of initial reader's results.
Vertically: Second reader's correction of initial over-diagnoses.

Reader	*1*	*3*	*4*	*8*	*9*	*10*	*11*	*13*	Correction of over-diagnoses on second reading of initial reader's results and number of photofluorograms checked
1		0/214 0.0 %	0/122 0.0 %	7/307 2.3 %	11/395 2.8 %	0/27 0.0 %	2/243 0.8 %	2/374 0.5 %	22/1,682 1.3 % 125,760
3	4/229 1.7 %		0/1,260 0.0 %	7/862 0.8 %	67/1,948 3.4 %	0/51 0.0 %	5/962 0.5 %	3/1,081 0.3 %	86/6,393 1.3 % 265,978
4	5/258 1.9 %	8/954 0.8 %		4/1,605 0.2 %	13/850 1.6 %	0/72 0.0 %	0/474 0.0 %	15/1,726 0.9 %	45/5,939 0.8 % 248,616
8	36/361 10.0 %	10/1,610 0.6 %	12/1,030 1.2 %		78/1,343 5.8 %	0/19 0.0 %	22/1,129 1.9 %	48/3,537 1.4 %	206/9,029 2.3 % 258,554
9	0/158 0.0 %	4/1,214 0.3 %	0/611 0.0 %	2/911 0.2 %		0/12 0.0 %	0/296 0.0 %	0/1,198 0.0 %	6/4,400 0.1 % 196,690
10	3/8 —	0/24 0.0 %		0/1 —	0/31 0.0 %		0/24 0.0 %	1/57 1.8 %	4/145 2.8 % 7,008
11	17/422 4.0 %	1/590 0.2 %	10/332 3.0 %	2/763 0.3 %	21/497 4.2 %	0/36 0.0 %		45/1,766 2.5 %	96/4,406 2.2 % 143,241
13	46/357 12.9 %	3/2,062 0.1 %	4/1,383 0.3 %	9/2,066 0.4 %	54/1,472 3.7 %	2/51 3.9 %	14/1,146 1.2 %		132/8,537 1.5 % 255,963
Second reader's correction of initial over-diagnoses and number of photofluorograms checked	111/1,793 6.2 % 84,080	26/6,668 0.4 % 239,513	26/4,738 0.5 % 162,318	31/6,515 0.5 % 238,443	244/6,536 3.7 % 258,538	2/268 0.7 % 13,912	43/4,274 1.0 % 166,136	114/9,739 1.2 % 338,870	597/40,531 1.5 % 1,501,810

Just as these values indicate the diagnostic gain from dual reading, so do they reveal the substantial inter-individual differences in the evaluation of photofluorograms.—It was not possible, however, to check the roentgenologic and clinical findings in the additional follow-up cases detected at second reading. Nor was it possible to find out if the amended over-diagnoses actually concerned negative or insignificant pulmonary findings, since all diagnoses were based solely on photofluorographic findings. Hence there was no means of deciding which of the interpreters evaluated his photofluorograms most effectively with regard to adequate diagnosis from the standpoint of preventive medicine.

Results in the Test Material

Evaluation of Test Photofluorograms

The 99 test cases distributed among 3,169 other photofluorograms showed pulmonary lesions which had not only been, 1–2 years earlier, detected and interpreted as follow-up cases, then verified roentgenologically, but had subsequently been found clinically to consist of active pulmonary diseases requiring treatment.

Results after Single Reading

The results after independent initial reading are detailed in table 11. The readers diagnosed between 27 and 81 of the 99 test cases as follow-up cases, the average score being 61 per cent and the range 27–82 per cent. By the same token, under-diagnoses averaged 39 per cent and had a range of

Table 11. Individual results of independent single reading in relation to correct identification and interpretation of the test cases.

Reader	*1*	*3*	*4*	*8*	*9*	*11*	*13*	*10*
1. Total number of test cases observed by one reader	42	49	60	64	73	77	79	83
2. Number of correctly identified but inadequately interpreted test cases with reference to verified clinical significance	15	7	5	4	5	3	1	2
3. Number of adequately interpreted test cases with reference to verified clinical diagnosis	27	42	55	60	68	74	78	81

18–73 per cent. A noteworthy finding was that the readers, with the exception of no. 10, showed the same grading as that which, in table 9, is based on the frequency of underestimated follow-up cases in the general material.

This grading was even retained when it was solely a matter of identifying pathologic changes on the test photofluorograms, without regard to their adequate evaluation as follow-up cases. The readers detected between 42 and 84 per cent of the test cases, the average being 66 per cent; in other words, they completely missed 16–58 per cent, or an average of 34 per cent, on single reading.

Since the various readers' interpretations did not necessarily concern identical test cases, a survey is given in table 12, showing the number of readings that led to the same evaluation. It will be observed that all eight interpreters together evaluated 89 test photofluorograms, or 90 per cent, as follow-up cases. General agreement on the diagnosis was reached, however, in only 18.2 per cent of the test cases; 8.1 per cent of them were regarded as follow-up cases only by one reader. Ten positive findings on test photofluorograms were overlooked by all readers.

Table 12. Identical interpretations of test photofluorograms by eight physicians in independent single readings.

Number of identical interpretations of test photofluorograms	Number of test photofluorograms	% of test photofluorograms	Reader							
			1	*3*	*4*	*8*	*9*	*11*	*13*	*10*
8	18	18.2	18	18	18	18	18	18	18	18
7	16	16.1	4	13	15	16	16	16	16	16
6	16	16.1	3	6	10	14	16	15	16	16
5	15	15.1	1	3	9	7	11	15	15	14
4	6	6.1	1	1	2	1	6	5	5	3
3	6	6.1	—	1	1	2	1	3	5	5
2	4	4.1	—	—	—	1	—	2	2	3
1	8	8.1	—	—	—	1	—	—	1	6
0	10	10.1	—	—	—	—	—	—	—	—
Total	99	100	27	42	55	60	68	74	78	81

The photofluorographic findings were grouped in accordance with the N.T.A. classification based on the extent of the pulmonary lesions (see page 19); in this way, they were classified with respect to the degree of difficulty

which their observation and evaluation might present. The results after independent single reading of the various groups are summarized in table 13.

It is found that only five readers evaluated all four test findings of *far advanced* pulmonary lesions as follow-up cases. One reader considered two of these cases insignificant, and readers 3 and 4 each interpreted one case as insignificant. Thus the interpreters even differed in their evaluations of far advanced lesions.

Table 13. Number of adequate interpretations of test photofluorograms after grouping of pathologic findings according to N.T.A. classification.

Grouping of pulmonary lesions according to N.T.A. classification	Number of test photofluorograms	%	Reader 1	3	4	8	9	11	13	10	Mean number of adequate interpretations
Far advanced pulmonary lesions	4	4	2	3	3	4	4	4	4	4	3.5
Moderately advanced pulmonary lesions	30	30	12	18	24	24	26	28	27	29	23.5
Minimal pulmonary lesions	65	66	13	21	28	32	38	42	47	48	34.9
Total	99	100	27	42	55	60	68	74	78	81	60.6

Similar discrepancies between the readers were found in evaluation of the 30 test cases with *moderately advanced* pulmonary lesions. Individually the interpreters regarded between 12 and 29 of these test findings as follow-up cases; none evaluated all cases adequately. At single reading, from one to 18, or 3–60 per cent, of the test findings were either overlooked or underestimated. On the average 23.5, or 77.6 per cent, of the moderately advanced lesions on the test photofluorograms were regarded as follow-up cases. Since, however, the readers did not necessarily detect the same cases, each test photofluorogram in this group was evaluated as a follow-up case at least once (table 14).

Only 8, or 26.7 per cent, of the test cases with moderately advanced lesions were uniformly evaluated by all readers. Two photofluorograms in this group were regarded by only one interpreter as follow-up cases. Table 14 demonstrates how the degree of concordance fell, and shows that even when the

Table 14. Identical interpretations of moderately advanced pulmonary lesions on test photofluorograms by eight physicians in single reading.

Number of identical inter-pretations of test photofluoro-grams	Number of test photo-fluoro-grams	% of test-photofluoro-grams	Reader							
			1	*3*	*4*	*8*	*9*	*11*	*13*	*10*
8	8	26.7	8	8	8	8	8	8	8	8
7	8	26.7	1	8	7	8	8	8	8	8
6	7	23.3	2	1	5	6	7	7	7	7
5	4	13.3	1	1	3	1	2	4	4	4
4	1	3.3	—	—	1	1	1	1	—	—
3	0	0.0	—	—	—	—	—	—	—	—
2	0	0.0	—	—	—	—	—	—	—	—
1	2	6.7	—	—	—	—	—	—	—	2
0	0	—	—	—	—	—	—	—	—	—
Total	30	100	12	18	24	24	26	28	27	29

cases were classified according to the number of identical evaluations the readers still retained the same grading.

These inter-individual differences were even more striking in evaluation of the test cases with *minimal pulmonary* lesions (table 15). The individual results varied between 13–48, or 20–74 per cent, adequate evaluations of the 65 test photofluorograms in this group. In other words, an average of only 52 per cent of minimal pulmonary lesions on the test photofluorograms were detected (mean number 33.6). From 26 to 80 per cent of these pulmonary lesions were accordingly underestimated on single reading.

It is evident from the table that in the evaluation of minimal lesions as follow-up cases, all readers were in agreement on only 8, or 12.3 per cent, of the test cases; while 6, or 9.3 per cent, were regarded as positive findings by only one interpreter. Since the diagnoses concerned different cases, altogether 55 of the 65 test photofluorograms were evaluated at least once as follow-up cases. All readers thus overlooked 10, or 15.3 per cent, of the test photofluorograms with minimal pulmonary lesions. On grouping of the test findings according to the number of identical evaluations, the same grading of the readers once more emerged.

The results of independent single reading accordingly demonstrate substantial individual discrepancies with respect to adequate evaluation of the

Table 15. Identical interpretations of minimal pulmonary lesions on test photofluorograms by eight physicians in single reading.

Number of identical interpretations of test photofluorograms	Number of test photofluorograms	% of test-photofluorograms	Reader							
			1	*3*	*4*	*8*	*9*	*11*	*13*	*10*
8	8	12.3	8	8	8	8	8	8	8	8
7	8	12.3	3	5	8	8	8	8	8	8
6	7	10.8	1	4	4	6	7	6	7	7
5	11	16.9	—	2	6	6	9	11	11	10
4	5	7.7	1	1	1	—	5	4	5	3
3	6	9.3	—	1	1	2	1	3	5	5
2	4	6.1	—	—	—	1	—	2	2	3
1	6	9.3	—	—	—	1	—	—	1	4
0	10	15.3	—	—	—	—	—	—	—	—
Total	65	100	13	21	28	32	38	42	47	48

Table 16. Results after independent dual reading of 99 test photofluorograms by eight physicians.

Reader	Number of adequate interpretations of test photofluorograms on single reading	Number of adequate interpretations on dual reading — Reader								Mean number of adequate interpretations after dual reading
		1	*3*	*4*	*8*	*9*	*11*	*13*	*10*	
1	27	—	50	59	63	69	75	78	81	67.8
3	42	50	—	64	65	71	76	78	82	69.4
4	55	59	64	—	70	72	76	80	84	72.1
8	60	63	65	70	—	73	79	82	85	73.6
9	68	69	71	72	73	—	77	79	86	75.2
11	74	75	76	76	79	77	—	80	86	78.4
13	78	78	78	80	82	79	80	—	87	80.6
10	81	81	82	84	85	86	86	87	—	84.4
Mean	60.6									75.8

test findings. This disparity even applied to interpretation of cases with far advanced pulmonary lesions but was greatest in evaluation of minimal lesions. The frequency of adequate evaluations and misinterpretations of identical test findings was consistent with the earlier grading of the readers on the basis of their percentages of initial under-diagnoses in the general photofluorographic material.

Results of Independent Dual Reading

By combining the readers' initial findings in pairs, the results of the different pseudoteams on independent dual reading were obtained. These were composed of the numbers of identical evaluations and the numbers of evaluations made by each member of a pseudoteam. In table 16 will be found the results obtained at independent dual reading of the test cases by all combinations of pairs.

The results of the different pairs are consistently better than those of individual reading. On independent dual reading, between 50 and 87, or 51–88 per cent, of the test findings were evaluated as follow-up cases. On the average, an adequate evaluation was thus recorded in 76 per cent of the cases. However, the different pairs showed greatly divergent results, due to the discrepancy in the number of adequate evaluations made by the respective members. The results of some pseudoteams approximated the individual results of one member. With some pairs, therefore, the reciprocal implementation on independent dual reading must have been due to the preponderance of additional evaluations in one reader's "position". In table 17 is shown the diagnostic gain from independent dual reading by the different combinations of pairs in relation to the single reading results.

It is quite evident that the results of dual reading were largely dependent on the quality of the two initial reading results. In some combinations of high scoring and low scoring individual results, the diagnostic gain was due solely to the numbers of additional evaluations made only by one reader. The reciprocal implementation by additional findings, on the other hand, was relatively low when high scoring individual results were combined. The combination of low scoring results does not, however, seem to have been very effective, despite the increased number of adequately evaluated test findings; for not even the average result in single reading of the test photofluorograms was attained.

Since the interpreters, on single evaluation of classified pulmonary lesions, had arrived at varying diagnoses, it was sought to establish whether dual reading improved the diagnostic accuracy. The results of the various pseudoteams on evaluation of the test photofluorograms after classification according to N.T.A. will therefore be reported in detail.

Table 17. Gains from dual reading of test photofluorograms. Number of adequate interpretations of test photofluorograms on single reading, and additional number on second reading.

Reader	Interpretations of test photo-fluorograms		Additional adequate interpretations on dual reading								Mean number of adequate interpretations added on dual reading
	Adequate interpretations on single reading	Missed on single reading	Reader								
			1	*3*	*4*	*8*	*9*	*11*	*13*	*10*	
1	27	72	—	23	32	36	42	48	51	54	40.8
3	42	57	8	—	22	23	29	34	36	40	27.4
4	55	44	4	9	—	15	17	21	25	29	17.1
8	60	39	3	5	10	—	13	19	22	25	13.8
9	68	31	1	3	4	5	—	9	11	18	7.3
11	74	25	1	2	2	5	3	—	6	12	4.4
13	78	21	0	0	2	4	1	2	—	9	2.6
10	81	18	0	1	3	4	5	5	6	—	3.4
Mean	60.6	38.4	2.4	6.1	10.7	13.1	15.7	19.7	22.4	26.7	16.7

On single reading of the four test findings with *far advanced* pulmonary lesions, reader 1 overlooked two, and each of readers 3 and 4 one test case. Since all the other readers evaluated all four as follow-up cases, only the possible combinations and the dual reading results of those interpreters are tabulated below.

Reader	Number of adequate interpretations on single reading	Number of adequate interpretations on dual reading Reader 1	3	4
1	2	—	3	3
3	3	3	—	4
4	3	3	4	—

It will be seen that on combination of reader 1 with readers 3 and 4, one of the four test cases was missed, whereas readers 3 and 4 together in a pseudoteam evaluated all four findings adequately as follow-up cases. When any of these three readers was combined with any of the others, all four cases were of course evaluated adequately.

Table 18. Results after independent dual reading of 30 photofluorograms with moderately advanced pulmonary lesions.

Reader	Number of adequate interpretations of photofluorograms on single reading	Number of adequate interpretations on dual reading Reader *1*	*3*	*4*	*8*	*9*	*11*	*13*	*10*	Mean number of photofluorograms
1	12	—	21	26	26	27	28	27	29	26.2
3	18	21	—	27	25	27	28	27	29	26.2
4	24	26	27	—	28	27	28	27	30	27.6
8	24	26	25	28	—	27	28	27	30	27.3
9	26	27	27	27	27	—	28	27	30	27.6
11	28	28	28	28	28	28	—	28	30	28.3
13	27	27	27	27	27	27	28	—	29	27.6
10	29	29	29	30	30	30	30	29	—	29.6
Mean	23.5									27.4

Table 18 presents the results of independent dual readings of test photofluorograms with *moderately advanced* pulmonary lesions. The various pseudoteams evaluated between 21 and 30, or 70–100 per cent, of the 30 test findings as follow-up cases. On the average 27.4, or 90 per cent, were interpreted adequately. In independent dual reading, therefore, between 0 and 30 per cent of the test cases were missed by the pseudoteams. The diagnostic gain from dual reading is also evident on combination of low scoring results, the reciprocal implementation of which by additional evaluations in positions led to a substantial improvement. Here, too, the complementary effect of dual reading was due to the greater number of adequate evaluations made by one reader. The additional evaluations of the different readers in the respective pairs are detailed in table 18.

On combination of high scoring and low scoring results, it once more emerges that the implementation by additional adequate evaluations in the latter was insignificant, and that the final results of these pseudoteams largely accorded with the higher individual result. Only four combinations showed adequate evaluation of all 30 test cases with moderately advanced pulmonary lesions.

The group of test cases with *minimal* pulmonary lesions consisted of 65 photofluorograms. As mentioned in the foregoing, ten (15 per cent) of these findings had been missed by all eight interpreters on single reading.—On combination of the various individual results these cases cannot, therefore, be detected; the results of the pseudoteams can be analyzed only on the basis of the 55 test findings that were evaluated as follow-up cases by at least one of the eight readers. Some limitation of the potentialities of independent dual reading is evident here; for some positive findings are bound to be missed inasmuch as they were overlooked by all interpreters on single reading. The effect of independent dual reading as regards the adequate evaluation of the 55 test photofluorograms in this group is shown in table 20.

Here the superiority of dual to single reading is once again manifest. There were conspicuous differences in the results of the various pseudoteams. Between 26 and 54, or 47–98 per cent, of the 55 test findings were detected by dual reading and evaluated adequately as follow-up cases. It follows that on combination of readers who apparently evaluated only obvious and extensive pulmonary lesions as follow-up cases, up to 53 per cent of active minimal pulmonary lesions on test photofluorograms were missed. Yet not one pair of interpreters regarded all 55 test findings as follow-up cases; this because some of the lesions were detected solely by readers who otherwise had low figures for adequate evaluations of test cases. The improvement of results and the reciprocal implementation of positive findings on independent dual reading are most evident from a comparison of the numbers of additional adequate evaluations made by the various readers.

Table 19. Gains from dual reading of test photofluorograms with moderately advanced pulmonary lesions. Number of adequate interpretations on single reading and additional number on second reading.

Reader	Interpretations of test photofluorograms: Adequate interpretations on single reading	Interpretations of test photofluorograms: Missed on single reading	Additional adequate interpretations on dual reading — Reader 1	3	4	8	9	11	13	10	Mean number of adequate interpretations added on dual reading
1	12	18	—	9	14	14	15	16	15	17	14.2
3	18	12	3	—	9	7	9	10	9	11	8.3
4	24	6	2	3	—	4	3	4	3	6	3.6
8	24	6	2	1	4	—	3	4	3	6	3.2
9	26	4	1	1	1	1	—	2	1	4	1.6
11	28	2	0	0	0	0	0	—	0	2	0.3
13	27	3	0	0	0	0	0	1	—	2	0.4
10	29	1	0	0	1	1	1	1	0	—	0.6
Mean	23.5	6.5	1.1	2.0	4.1	3.8	4.4	5.4	4.4	7.0	4.6

Table 20. Results after independent dual reading of 65 photofluorograms with minimal pulmonary lesions.

Reader	Number of adequate interpretations of photofluorograms on single reading	Number of adequate interpretations on dual reading — Reader 1	3	4	8	9	11	13	10	Mean number of photofluorograms
1	13	—	26	29	33	38	43	48	48	36.4
3	21	26	—	33	39	40	43	47	49	39.5
4	28	29	33	—	38	41	44	48	50	40.4
8	32	33	39	38	—	42	47	50	51	42.8
9	38	38	40	41	42	—	45	47	52	43.5
11	42	43	43	44	47	45	—	48	52	46.0
13	47	48	47	48	50	47	48	—	54	48.8
10	48	48	49	50	51	52	52	54	—	50.8
Mean	33.6									43.5

It will be seen from table 21 that the average number of additional positive findings referable to the one half of the readers was more than ten times greater than that referable to the other. On the whole, the implementary findings were greater on combination of low scoring readers than on combination of high scoring readers, due to the fact that the former evaluated so many different test cases. This suggests a substantial inter-individual difference between these readers in their attitude to relatively small pulmonary lesions, and especially minimal ones. Hence the reciprocal implementation served to increase by many times the number of adequate evaluations in some series with few initial positive findings. The diagnostic gain from combination of high scoring readers, on the other hand, was proportionally smaller, since their evaluations usually related to identical cases. However, the effect of dual reading was more evident here than in the evaluation of moderately advanced pulmonary lesions.

The results after independent dual reading of test photofluorograms showed a very marked superiority to those of single reading by the various interpreters. Even on combination of low individual results, there was a reciprocal implementation of such magnitude as to cancel out much of the observer error associated with single reading. This latter was found to be handicapped by

Table 21. Gains from dual reading of test photofluorograms with minimal pulmonary lesions. Number of adequate interpretations on single reading, and additional number on second reading.

Reader	Interpretations of test photofluorograms: Adequate interpretations on single reading	Interpretations of test photofluorograms: Missed on single reading	Additional adequate interpretations on dual reading — Reader *1*	*3*	*4*	*8*	*9*	*11*	*13*	*10*	Mean number of interpretations added by dual reading
1	13	52	—	13	16	20	25	30	35	35	24.8
3	21	44	5	—	12	18	19	22	26	28	18.6
4	28	37	1	5	—	10	13	16	20	22	12.4
8	32	33	1	7	6	—	10	15	18	19	10.9
9	38	27	0	2	3	4	—	7	9	14	5.6
11	42	23	1	1	2	5	3	—	6	10	4.0
13	47	18	1	0	1	3	0	1	—	7	1.8
10	48	17	0	1	2	3	4	4	6	—	2.8
Mean	33.6	31.4	1.3	4.1	6.0	9.0	10.6	13.6	17.1	19.2	10.1

subjective errors leading to such a high under-diagnosis rate—at least with regard to adequate evaluation of the test cases—that dual reading must be regarded as a *sine qua non* for more efficient interpretation of photofluorograms in mass chest surveys.

It emerged from the test that the reciprocal implementation of findings by readers in pseudoteams was usually due to the greater number of adequate evaluations made by one member of each pair. The incidence of these additional findings rose with the readers' grades, irrespective of the types of pulmonary lesions interpreted. The efficiency of dual reading varied with the magnitude of the respective pairs' joint observer error. Some pseudoteams did not even attain the average result of single readings by all eight interpreters. The discrepancy in results between the different pairs was greatest for evaluation of minimal pulmonary lesions, where under-estimation or overlooking of cases was commonest. Neither did independent multiple readings disclose cases that had been missed by all interpreters on single reading. Ten photofluorograms with minimal pulmonary lesions still remained undetected after eight readings by all interpreters in the test material.—It seems evident, therefore, that some active pulmonary lesions may even be overlooked after multiple readings of any other photofluorographic material. —Since these ten cases had originally been detected by one or another of the interpreters in the test group, it would appear that an intra-individual variability in evaluation of relatively small pulmonary lesions was responsible for the inconsistent findings of the same readers on different occasions (see page 63).

Dual Reading of Known Initial Results

When the readers had interpreted the entire test material independently of each other, they began checking one another's results. This second reading conformed to the method described in the foregoing, each interpreter checking a number of the initial results of his colleagues. It comprised 40 of the 56 possible combinations. The results are detailed in table 22, and they chiefly envisage the numbers of additional positive findings in positions.

It will be seen that the reciprocal corrections in the different positions when the readers were cognizant of each other's initial results, had more or less the same outcome as that of independent dual reading of the test cases (*cf.* table 17). Indeed, a few combinations of pairs showed even better results. The total number of additional positive findings was just as high as that in independent dual reading by the relevant combinations of interpreters (see table 23). Readers who themselves had poor initial results corrected those of their colleagues to a relatively small extent; and vice versa.

It was found, however, that some interpreters had a greater or smaller

Table 22. Gains from dual reading of known results after initial evaluation of test photofluorograms. Number of adequate interpretations of test photofluorograms on single reading, and additional number on second reading.

Reader	Interpretations of test photofluorograms		Additional adequate interpretations on dual reading of known initial results								Mean number of adequate interpretations added on dual reading
	Adequate interpretations on single reading	Missed on single reading	Reader								
			1	*3*	*4*	*8*	*9*	*11*	*13*	*10*	
1	27	72	—	—	44	55	—	—	52	56	51.7
3	42	57	1	—	16	18	31	37	21	—	20.7
4	55	44	—	2	—	—	30	31	29	—	23.0
8	60	39	—	0	—	—	23	13	—	19	13.7
9	68	31	—	0	13	1	—	9	7	10	6.7
11	74	25	4	1	—	3	6	—	4	5	3.8
13	78	21	0	1	8	—	3	1	—	8	3.5
10	81	18	0	—	—	1	4	—	4	—	2.2
Mean	60.6	38.4	1.2	0.8	20.2	15.6	16.1	18.2	19.5	19.6	14.3

Table 23. Summary of adequate interpretations of test photofluorograms by pairs of readers on independent dual reading and on checking known initial results with reference to second reader's intra-individual variability.

Combinations of second and first readers	Number of test photofluorograms adequately interpreted		Number of second reader's additional interpretations	Ratio of second reader's additional findings to his personal findings in pseudoteam	Ratio of second reader's additional findings to test cases overlooked on dual reading by pseudoteam
	on independent dual reading (pseudoteam)	on checking known initial results			
1 : 3	50	43	1	1/8	0/49
1 : 11	75	78	4	1/1	3/24
1 : 13	78	78	0	0/0	0/21
1 : 10	81	81	0	0/0	0/18
	284	*280*	*5*	*2/9* —	*3/112* (2.7 %)
3 : 4	64	57	2	1/9	1/35
3 : 8	65	60	0	0/5	0/34
3 : 9	71	68	0	0/3	0/28
3 : 11	76	75	1	1/2	0/23
3 : 13	78	79	1	0/0	1/21
	354	*339*	*4*	*2/19* (10.5 %)	*2/141* (1.4 %)
4 : 1	59	71	44	28/32	16/40
4 : 3	64	58	16	11/22	5/35
4 : 9	72	81	13	4/4	9/27
4 : 13	80	86	8	2/2	6/19
	275	*296*	*81*	*45/60* (74.3 %)	*36/121* (29.7 %)
8 : 1	63	82	55	35/36	20/36
8 : 3	65	60	18	13/23	5/34
8 : 9	73	69	1	1/5	0/26
8 : 11	79	77	3	3/5	0/20
8 : 10	85	82	1	0/4	1/14
	365	*370*	*78*	*52/73* (71.2 %)	*26/130* (20.0 %)

9 : 3	71	73	31	26/29	5/28
9 : 4	72	85	30	16/17	14/27
9 : 8	73	83	23	13/13	10/26
9 : 11	77	80	6	3/3	3/22
9 : 13	79	81	3	0/1	3/20
9 : 10	86	85	4	4/5	0/13
	458	*487*	*97*	*62/68 (91.2 %)*	*35/136 (25.7 %)*
11 : 3	76	79	37	30/34	7/23
11 : 4	76	86	31	21/21	10/23
11 : 8	79	73	13	11/19	2/20
11 : 9	77	77	9	6/9	3/22
11 : 13	80	79	1	1/2	0/19
	388	*394*	*91*	*69/85 (81.2 %)*	*22/107 (20.6 %)*
13 : 1	78	79	52	48/51	4/21
13 : 3	78	63	21	19/36	2/21
13 : 4	80	84	29	24/25	5/19
13 : 9	79	75	7	7/11	0/20
13 : 11	80	78	4	4/6	0/19
13 : 10	87	85	4	2/6	2/12
	482	*464*	*117*	*104/135 (77.0 %)*	*13/112 (11.6 %)*
10 : 1	81	83	56	51/54	5/18
10 : 8	85	79	19	18/25	1/14
10 : 9	86	78	10	9/18	1/13
10 : 11	86	79	5	5/12	0/13
10 : 13	87	86	8	5/9	3/12
	425	*405*	*98*	*88/118 (74.6 %)*	*10/70 (14.2 %)*
Total	*3,031*	*3,035*	*571*	*424/567 (74.8 %)*	*147/929 (15.7 %)*
Mean number of adequate interpretations of test photofluorograms	*75.8*	*75.9*			

number of additional findings than that on independent dual reading in the corresponding combination. This implies that the second readers either missed a number of test cases which they had themselves noted at the initial reading, or evaluated as follow-up cases some test findings which they had initially overlooked. When the latter cases had also been overlooked originally, the same interpreters, acting as second readers, must have evaluated them differently on different occasions. In this investigation the second reading of known initial results thus disclosed not only the varying efficiency of the readers in augmenting each other's findings, but also their intra-individual variability when evaluating identical test cases on different occasions.

Calculation of the results after independent dual reading by the various pseudoteams revealed the numbers of additional test findings which each member of the respective pairs alone evaluated as follow-up cases. When the same interpreter corrected the known initial results of another, he was confronted with a known number of test photofluorograms that had been under-estimated by the first reader. It was also known, however, that the checking interpreter regarded these findings as follow-up cases when he himself read the test series. He could be expected to evaluate them consistently with his own initial results when they were under-estimated in the checked material. On the other hand, the possibility existed that a checking interpreter would evaluate as follow-up cases some test findings that he and his partner in a given pseudoteam would have missed. Inasmuch as the results of independent dual reading varied from 50 to 87 of 99 possible adequate evaluations, between 12 and 49 test cases were consequently overlooked by both members of the corresponding pseudoteam. The number of possibilities for correction of such jointly missed cases was thus dependent on the calculated results of the pair at independent dual reading.

Table 23 surveys the results of the different pairs of interpreters after independent dual reading and after checking of known initial results. Aside from the total number of additional positive findings recorded by the checking readers, it shows the proportion of corrections in relation to additional findings that were adequately evaluated by the second reader in the same combination on independent dual reading. Also given is the number of test cases overlooked by the respective pairs at independent dual reading, and the number of them detected by the second readers when checking known initial results.

In this test the interpreters thus not only checked other readers' initial results of which they were cognizant; they also read several times, independently, that part of their personal findings which had been overlooked by the respective first readers, as well as such test cases as had been missed by both interpreters at independent dual reading.

In table 23 will be seen the *intra-individual variations of each reader on*

multiple evaluation of the test photofluorograms. On second reading the interpreters redetected between 10.5 and 91.2 per cent of their personal additional findings at independent dual reading by the respective combinations of pairs, and from 1.4 to 29.7 per cent of test cases that had been overlooked by the relevant pseudoteams.—The intra-individual variation thus appears to be of major importance in the observation and evaluation of pulmonary lesions on photofluorograms.

In 40 second readings, all interpreters together had a total of 567 possibilities for evaluating identically the test cases which they had themselves regarded as follow-up cases on first reading of the test series. In 424, or 74.8 per cent, of these 567 possibilities the evaluation was consistent with the readers' initial results. At the same time there were 929 possibilities of evaluating as follow-up cases such test findings that had been overlooked by the various pairs of interpreters at independent dual reading. On 147, or 15.6 per cent, of the occasions these test findings were regarded as follow-up cases on checking of known initial results.

Corrections of initial results were accordingly made in 571 instances during 40 second readings. A total of 424, or 74.3 per cent, of these corrections were in agreement with the second readers' own initial results; and in 147, or 25.7 per cent, of the corrections the checking interpreters evaluated as follow-up cases test findings that they had overlooked, together with the relevant first readers in various pseudoteams on independent dual reading.

Comparison of the adequate evaluations of test findings by the forty pairs of interpreters, as pseudoteams, on independent dual reading and, in practice, on second reading of known initial results indicates that the two methods were equal in effectiveness. On the average, 75.8 and 75.9 test cases respectively were adequately evaluated with the two dual reading methods (see table 23).

On checking of known initial results, five test cases were detected of the ten that had been missed by all eight interpreters at the initial reading (test photofluorograms nos. 44, 50, 59, 71 and 83). Table 24 shows the numbers of readings of these test photofluorograms by each interpreter, and the number of evaluations as follow-up cases.

These five test findings were classified solely as minimal pulmonary lesions. The readers who did observe them were clearly somewhat hesitant and uncertain about their interpretation; this is evident from the varying frequency of their evaluation as follow-up cases. Bearing in mind that after a total of 48 readings by eight interpreters, five of the ten test cases were still undetected, it seems justified to assume that at the original dual reading 1–2 years earlier, they had been observed purely by chance.

Table 24. Number of additional adequate interpretations after multiple evaluation of ten test photofluorograms missed on single reading by all readers.

Reader	Number of readings	Number of adequate interpretations No. of test photofluorogram 44	50	59	71	83
1	5	0	0	0	0	0
3	6	0	0	0	0	0
4	5	0	3	0	3	2
8	6	0	0	1	0	0
9	7	0	0	0	0	1
11	6	2	3	0	0	2
13	7	0	0	0	0	1
10	6	1	4	0	0	0
Total	48	3	10	1	3	6

Intra-Individual Variability in Evaluation of Test Photofluorograms

Since identical test photofluorograms were evaluated differently by the same interpreter on different occasions, the original diagnoses of test cases by the eight readers during the mass survey of 1955–1956 in Stockholm, were compared with their evaluations during the test. All pulmonary lesions on test photofluorograms were found to have been regarded as follow-up cases by one of the eight interpreters either at first or second reading. The test cases were thus referable to the different interpreters according to either of these alternatives. When, during the test, a reader was confronted with a test photofluorogram which he had himself regarded as a follow-up case 1–2 years earlier, an identical evaluation could be expected. At the same time the cases were not likely to be recognized so long afterwards. When the original evaluations were then compared with the subsequent test interpretations, some idea would be gained of the significance of the intra-individual variability in photofluorogram reading. The results of this test are detailed in table 25.

In the table are given first the number of photofluorographic findings which each interpreter had originally regarded as follow-up cases in his capacity of first reader, as well as the number of those which he evaluated identically during the test. Then follow the numbers of test photofluorograms the initial evaluation of which as follow-up cases had been endorsed by each interpreter acting as original second reader, as well as the numbers that he evaluated identically in the test. Lastly, the numbers of test cases are indicated

that had been overlooked by some interpreters acting as original first readers, together with the numbers that were again missed during the test.

It is found that the interpreters once more evaluated as follow-up cases 42, or 68 per cent, of the 62 test findings which they had originally detected in the capacity of first readers. Some interpreters re-evaluated only 33 and 40 per cent of their test photofluorograms in accordance with their earlier diagnoses.—Of the 48 test photofluorograms the initial evaluation of which as follow-up cases they had endorsed in the capacity of second readers, they redetected only 29, or 60 per cent, during the test. On the other hand, some interpreters overlooked in the test only five of the ten follow-up cases which they had missed at the original first reading.

The above results illustrate the intra-individual variability in evaluation of pathologic changes on test photofluorograms that concerned clinically significant active pulmonary disease. It is noteworthy that test photofluorograms were evaluated differently not only by different readers but also by the same readers on different occasions. It would seem, however, that even the intra-individual variability in evaluation of these photofluorograms could be graded as in the preceding results.

Results after Evaluation of the Remaining Test Material

The total test material comprised 3,268 pulmonary photofluorograms in anteroposterior and lateral projection, including the 99 test cases. In the following will be reported, after evaluation of the test photofluorograms, the results obtained on checking of the remaining 3,169, which were read according to the same norms. This series automatically followed from the selection of film rolls containing the test photofluorograms. The number of positive findings therein is unknown and can only be estimated from the eight readers' results. However, the individual results may show whether the interpreters differed to the same extent as they had done when reading the general photofluorographic material from the mass surveys of 1953—1956, or when evaluating the test photofluorograms.

In table 26 are presented the results of *independent single reading* of the remaining 3,169 photofluorograms. A total of 324 were evaluated by all eight readers as positive findings. There was, once more, a substantial difference between the individual results, which ranged from 73, or 2.3 per cent, to 210, or 6.6 per cent, positive findings. Worthy of note is that the incidence of positive evaluations made by the different readers rose almost proportionally to that in evaluation of the test cases. The individual results also reflected discrepancies similar to those found in reading of the general photofluorographic material. The mean number of follow-up cases amounted to 143.0 or

Table 25. Intra-individual variations of interpretations of identical test photofluorograms on different occasions.

Reader	Number of test photofluorograms interpreted as follow up cases on initial reading (1955–1956)	Number of identical interpretations during test	% of initial interpretations	Number of initial interpretations of test photofluorograms endorsed during control (1955–1956)	Number of identical interpretations during test	% of initially endorsed interpretations	Number of initially missed findings on test photofluorograms (1955–1956)	Number of identical interpretations during test
1	2	0	—*	4	0	—*	—	—
3	6	2	33	11	5	45	4	3*
4	1	1	—*	4	4	—*	1	0*
8	4	3	—*	0	—	—	—	—
9	20	8	40	14	9	64	—	—
11	8	7	87	6	5	83	—	—
13	14	14	100	8	5	62	—	—
10	7	7	100	1	1	—*	5	2*
Total	62	42	68	48	29	60	10	5

* Base too small for estimation of percentage.

about 4 per cent, of the 3,169 photofluorograms, which figure closely accords with the incidence of follow-up cases in mass chest examinations of the population of Stockholm. Only 33, or 10 per cent, of the 324 positive photofluorographic findings were evaluated identically by all interpreters; and 105, or 33 per cent, were interpreted as positive by only one reader. On grouping according to the number of identical evaluations, the readers tended to show the same grading as before.

Table 26. Initial results after single reading of remaining photofluorograms in test material.

Number of positive readings of photofluorograms	Number of photofluorograms	Reader							
		1	*3*	*4*	*8*	*9*	*11*	*13*	*10*
1	105	6	9	4	5	3	12	13	53
2	49	5	4	6	12	15	14	21	21
3	29	2	8	2	13	13	15	17	17
4	30	1	15	6	16	19	21	25	17
5	27	8	13	9	16	21	22	24	22
6	22	7	10	16	19	20	19	22	19
7	29	11	24	25	29	29	28	29	28
8	33	33	33	33	33	33	33	33	33
Total	324	73	116	101	143	153	164	184	210

Reciprocal Correction of Under-Diagnoses on Second Reading of Known Initial Results

In table 27 are shown the additional positive findings of the various interpreters on *reciprocal checking of known initial results.* This table reflects the same grading of readers as that in table 22; for low scoring results were generally implemented to an increasing degree with rising grades of the second readers, and vice versa. Some interpreters, however, appeared to lose their places in this grading, which pointed to some variability in their qualities as second readers.—The results of independent dual reading of the remaining test material were not evaluated because the general photofluorographic material had not been interpreted accordingly. Moreover, the information gained would have been unreliable inasmuch as the actual number of significant pulmonary lesions in the remaining material was not known.

Table 27. Additional positive interpretations of photofluorograms on dual reading of known initial results.

Reader	Number of positive interpretations of photofluorograms on single reading	Additional positive interpretations on dual reading — Reader *1*	*3*	*4*	*8*	*9*	*11*	*13*	*10*	Mean number of additional positive interpretations of photofluorograms on second reading
1	73	—	—	128	239	—	—	199	128	173.5
3	116	5	—	28	59	107	144	130	—	78.7
4	101	—	33	—	—	123	143	169	—	117.0
8	143	—	10	—	—	76	39	—	44	42.3
9	153	—	15	81	5	—	78	34	38	41.8
11	164	9	22	—	10	35	—	47	20	23.8
13	184	2	21	45	—	17	10	—	29	20.7
10	210	1	—	—	18	25	—	58	—	25.5
Mean	143.0	4.3	20.2	70.5	66.2	63.8	82.8	107.7	51.8	60.6

Results after Multiple Interpretations of the Remaining Test Material

The remainder of the test material was read, like the test photofluorograms, a total of 48 times, each interpreter doing an initial reading and then between four and six second readings. A reader who repeatedly interpreted the same series could be expected to evaluate some of these 324 photofluorograms as positive findings which he himself, at the first reading, had either overlooked or regarded as negative. In so doing, he would be endorsing the results of one or more of the other interpreters detecting the same cases.—It was first sought to ascertain if the degree of concordance in evaluation of these 324 photofluorograms increased after repeated interpretations of the same material (see table 28).

It is clear from the table that the concurrence in this respect did in fact increase very appreciably. The best evidence of this is that the number of photofluorographic findings that, after the first reading, were regarded as follow-up cases by only one reader, fell from 105 to 29. The number evaluated identically by five to seven readers increased, whereas the number with eight identical diagnoses remained unchanged at 33 (*cf.* table 26).

In repeated interpretations of the remaining test material a further 196 positive cases were nevertheless detected, so that the total number of follow-

Table 28. Results after repeated reading of 324 photofluorograms considered positive after single interpretation.

Number of positive readings	Number of photofluoro-grams	Reader 1	3	4	8	9	11	13	10
1	29	3	4	3	3	1	4	6	5
2	53	5	10	7	16	16	9	19	24
3	37	1	1	7	27	14	15	24	21
4	33	3	7	12	20	22	22	28	18
5	44	6	32	15	33	34	32	35	33
6	45	10	21	31	41	43	41	44	39
7	50	16	42	46	48	50	49	50	49
8	33	33	33	33	33	33	33	33	33
Total	324	77	150	154	221	213	205	239	222

up cases after 48 readings ultimately rose to 520, or 16.4 per cent, of the remaining material. When these 196 additional findings were classified according to the numbers of identical evaluations, 159 of them, or 76 per cent, were found to have been evaluated once only as follow-up cases. (Table 29.) The probability that these findings had been over-diagnosed seems to have

Table 29. Number of additional positive findings after repeated reading of remaining photofluorograms in test material.

Number of positive readings	Number of photofluoro-grams	Reader 1	3	4	8	9	11	13	10
1	159	2	12	36	27	5	41	20	16
2	29	1	5	12	8	3	18	8	3
3	6	—	1	4	2	1	3	4	3
4	1	—	—	1	1	—	1	—	1
5	1	—	—	1	1	1	1	1	—
6	—	—	—	—	—	—	—	—	—
7	—	—	—	—	—	—	—	—	—
8	—	—	—	—	—	—	—	—	—
Total	196	3	18	54	39	10	64	33	23

been relatively great. The number of additional findings in the individual results varied from three to 64. Whether this variability could be attributed to the readers' individual tendencies toward over-diagnosis was not clear.

These multiple interpretations were done in connection with the reciprocal checking of initial results for the purpose of correcting both under- and over-diagnosed cases. It was found, however, that the readers during the test corrected only under-diagnosed findings; hence it seems plausible to assume that the individual results after repeated interpretations of the rest of the material were marred by a relatively high over-diagnosis rate.

Table 30. Final results after 48 readings of photofluorograms in remaining test material by eight interpreters.

Number of positive readings	Number of photofluorograms	Reader							
		1	*3*	*4*	*8*	*9*	*11*	*13*	*10*
1	188	5	16	39	30	6	45	26	21
2	82	6	15	19	24	19	27	27	27
3	43	1	2	11	29	15	18	28	24
4	34	3	7	13	21	22	23	28	19
5	45	6	32	16	34	35	33	36	33
6	45	10	21	31	41	43	41	44	39
7	50	16	42	46	48	50	49	50	49
8	33	33	33	33	33	33	33	33	33
Total	520	80	168	208	260	223	269	272	245

In table 30 are detailed the final results after 48 interpretations of the remaining material. After five to seven readings per interpreter, the numbers of positive findings varied between 80 and 272. Yet still only 33, or 6 per cent, of the 520 photofluorograms were evaluated by all readers identically as follow-up cases; and 188, or 36 per cent, were regarded as positive by only one interpreter.

The difference between the initial and final individual results is shown in table 31. Aside from the conspicuous inter-individual differences, the intra-individual variability was also evident when the interpreters did repeated evaluations of the same series. After multiple readings, some readers found almost twice as many follow-up cases as they had done at initial reading. At the same time there was evidently a manifold increase in the number of photofluorograms which, originally, they alone had evaluated as positive (*cf.* tables 27 and 30).

Table 31. Additional positive findings on photofluorograms of the remaining test material after multiple readings.

	Number of readings	Number of positive photo-fluoro-grams	Individual results of readers								Mean number of positive interpretations of photo-fluoro-grams
			1	*3*	*4*	*8*	*9*	*11*	*13*	*10*	
Initial single reading	8	324	73	116	101	143	153	164	184	210	143.0
Repeated second reading	40	196	7	52	107	117	70	105	88	35	72.6
Total	48	520	80	168	208	260	223	269	272	245	215.6

The mean number of follow-up cases rose after all readings from 143.0 to 215.6, i.e., by about 50 per cent. Coincident with this substantial rise in positive findings there were detected, however, only five test cases that had been overlooked by all readers at the initial interpretation. After 48 readings there still remained, therefore, five undetected test cases.

In the remaining test material the various readers found, more or less proportionally to their usual results on evaluation of ordinary photofluorographic series, virtually equal rates of follow-up cases (*cf.* table 5, column I). The inter-individual variability was once more evident, both on initial interpretation of the same series and on second reading of known initial results with the attendant reciprocal corrections. The interpreters thus retained, on the whole, the same grading, irrespective of which photofluorograms they had read.

The incidence of positive findings was found to have risen appreciably during the 48 readings, and it is probable that the over-diagnosis rate increased proportionally to the number of newly detected follow-up cases. Yet these interpretations, remarkably enough, did not lead to adequate evaluation of all test cases, which consisted of active pulmonary lesions detected 1–2 years earlier on the same photofluorograms by the same readers. It seems justified to infer, therefore, that some active pulmonary lesions are likely to be overlooked in multiple interpretations of other photofluorographic series.

CHAPTER IV

Discussion and Conclusions

On the basis of the results reported in the foregoing, the practical corollaries as to the value of dual reading will now be discussed. Since the results of all reading methods are dependent on the qualities of the individual interpreters, the discussion will be primarily concerned with the observer error as noted in single reading and various forms of dual reading of the photofluorograms in this investigation. The efficiency of independent dual reading and checking of known initial results will then be compared, with respect to the diagnostic gain and the sources of error that must be expected with each method. The conclusions that follow the discussion of the various points will not be specially summarized since they derive from a local investigation. They nevertheless have a bearing on general problems that might be of interest to everyone concerned with mass photofluorographic surveys.

The investigation itself is founded on a study of the results after the reading of 2,084,583 photofluorograms by fourteen interpreters. In general, this series was so apportioned that each interpreter read a mixture of photofluorograms originating from all population groups throughout Sweden. In these circumstances it was remarkable that when the interpreters acted as initial readers, their positive findings varied as much as 1.3–3.8 per cent of their respective series (see table 5). When the total material had been evaluated for the second time, each reader's initial results being checked by most of his colleagues, these discrepancies between the initial readers' percentages of follow-up cases were not evened out. The implication was that the interpreters even might have differed in their capacities of second readers. It was found, however, that in the initial reading they had overlooked or misinterpreted between 2.9 and 27.8 per cent of the final numbers of follow-up cases; and, moreover, the over-diagnosis rate in the initial follow-up cases varied from 0.0 to 10.9 per cent. Analysis of their second reading results disclosed similar, though smaller differences; these too were statistically significant. The checking interpreters detected, in their respective series, between 0.0 and 12.6 per cent of the final numbers of follow-up cases and corrected over-diagnoses in 0.0 to 6.7 per cent of the initial follow-up cases (see table 6). The differences between the various readers with respect to the initial and the second reading results were in most instances statistically significant. Having regard to the importance of checking especially the under-diagnoses in mass chest examinations, the

various initial results were graded according to the under-diagnosis rates of the respective interpreters.—These rates varied within the same limits with respect to the results of the eight readers who participated in the test.

Since the clinical findings in the initially under-diagnosed follow-up cases were not available, it could only be concluded from the disparate results that the readers had either differed in their personal approach to photofluorogram interpretation or had not conformed to uniform standards in their evaluation of pathologic changes.

On the assumption that the various photofluorographic series had equivalent compositions, the question arose as to which mode of interpretation would best meet the aims of mass chest surveys. It was quite conceivable that an interpreter whom the other readers considered to have a high initial under-diagnosis rate had in fact evaluated his particular series more rationally than the others, simply by regarding as follow-up cases only those photofluorographic findings that really were of clinical significance. If this were true, then any findings added to his initial results by the checking interpreters would have been over-diagnosed. Nor was it possible to demonstrate that a reader with a high initial over-diagnosis rate might have evaluated pathologic findings inadequately.

The problem posed by the inter-individual difference between photofluorogram interpreters has been the subject of detailed investigations (GARLAND, 1950; YERUSHALMY *et al.*, 1951), which have been chiefly designed to test either the dependability of the photofluorographic technique or the qualities of the readers.

In 1956 NIELSEN conducted a test at the Center for the purpose of elucidating the interpreters' capability (NIELSEN, 1957). The task of the readers was to detect 78 artefacts in a series of 101 pulmonary photofluorograms, the artefacts being so arranged as to simulate pathologic pulmonary lesions. The test series was read independently by ten interpreters, nine of whom had also taken part in the reading of the general photofluorographic material (table 5). This test revealed some inter-individual discrepancies in common with the results after evaluation of the general material, and they are accordingly shown in table 32. The readers can be identified by the codification applied in the present investigation, while NIELSEN's original code numbers are given in parentheses.

The interpreters' scores are virtually consistent, in general, with their grading in table 5.—It should be pointed out, however, that 19 artefacts were not observed by any of the ten readers.

NIELSEN's test had been primarily designed to investigate the perception of the interpreters without regard to their evaluation of the findings. It was not even certain whether experienced readers accepted and noted as pulmonary lesions all the artefacts in this series.—Importance therefore attached to

Table 32. Results after reading of Nielsen's test series of 101 photofluorograms with 78 artefacts simulating pulmonary lesions. (After H. Nielsen)

Interpreters Code Number	False infiltrates identified Number	Percent of 59
1 (1)	24	41
4 (2)	26	44
8 (3)	31	53
3 (4)	34	58
9 (5)	39	64
*X** (6)	39	64
12 (7)	39	64
11 (8)	43	73
13 (9)	46	78
14 (0)	48	81
Average	37	63
Number of false infiltrates identified by at least one interpreter	59	100

* Reader X is an experienced interpreter of photofluorograms who was invited to participate in the test.

whether a reader would be inconsistent, and if so to what extent, in both his observations of lesions and his evaluation of them according to their clinical significance. Only on the basis of a photofluorographic series with clinically verified positive findings was it possible to find out which mode of interpretation was the most effective for detecting and evaluating such findings in accordance with the known clinical diagnosis.For this reason a test material was composed which included a number of clinically verified active pulmonary lesions. These represented, at the same time, a selection of pathologic findings newly detected during the second mass photofluorographic survey of 1955–1956 in Stockholm. With systematic sampling from both sexes and all age groups it could be assumed, moreover, that all types of pulmonary lesions first detected on repeated examination of the same population would be included among the test photofluorograms. The test material was similar to an ordinary photofluorogram series, and was also read under routine conditions. Each film roll included a test photofluorogram with a known diagnosis, aside from the remaining photofluorograms for which the diagnoses were unknown. The readers also had to evaluate these others according to the same

norms as those in the test cases. Their results in this remaining material could then be compared with those referable to the general series from 1953–1956, which were known inasmuch as most of the test interpreters had also taken part in reading it.

The aim of the test was to establish wether clinically significant photofluorographic findings would be evaluated identically by all of the readers, or whether there would be the same subjective differences that had emerged in reading of the general material. In addition, the effectiveness of independent dual reading as well as dual reading of known initial results was to be investigated and compared. Lastly, it was desired to find out if testing with a comparatively large series containing only occasional test cases, and testing with a relatively small series like NIELSEN's, in which the test photofluorograms were at closer intervals, yielded equivalent data on the readers' qualities and the effectiveness of different reading methods.

As regards the interpretation of test cases, the results disclosed marked differences between the readers in both their observation and their evaluation of pathologic changes (see table 11). In this respect, a clear distinction had to be made between adequate evaluation of a photofluorographic finding as a follow-up case and misinterpretation or overlooking thereof.—When a photofluorographic finding fails to be reported for follow-up, it does not lead to further clinical examination. Hence, misinterpretation of a finding is, in practice, tantamount to overlooking it.

On single reading of the test series the interpreters, it is true, observed between 42 and 83 of the 99 test cases, but they regarded only 27 to 81 of them as follow-up cases, the average thus being 61 per cent. This means that 18–72 test cases were underestimated on single reading. One reader in fact missed four times as many significant pulmonary lesions as another. The personal under-diagnosis rates were very similar to the initial ones in the general material, for they more or less fitted into the same grading pattern. Even the interpreters who had taken part in NIELSEN's test retained, on the whole, their original grades (see table 31).

At initial reading by the eight interpreters, the numbers of evaluations of test photofluorograms as follow-up cases could vary between zero and eight. A total of 89 of the 99 test photofluorograms were evaluated at least once as follow-up cases. Only 18, or 18 per cent, were regarded by all readers as follow-up cases. The interpreters were also unanimous, however, in negative evaluations of 10 test cases with active pulmonary lesions.

When the test photofluorograms were grouped in accordance with the N.T.A. classification based on the extent of pulmonary lesions, the interpreters' evaluations were found to be identical only for two of four far advanced pulmonary lesions; eight, or 27 per cent, of 30 moderately advanced pulmonary lesions; and eight, or 12 per cent, of 65 minimal pulmonary lesions

(see tables 14 and 15). The degree of concordance thus fell with decreasing extent of the lesions.—This lack of agreement seemed to reflect a variability in the readers' approach to photofluorogram interpretation. In these circumstances negative evaluation of a finding by the majority of readers did not necessarily mean that its positive evaluation by one reader alone was unjustified. Two, or 6 per cent, of moderately advanced pulmonary lesions and six, or 9 per cent, of minimal ones were regarded as follow-up cases by a single interpreter in accordance with the clinical diagnoses. Yet it was also clear that not even the negative evaluation of a photofluorogram by all readers in the test group unequivocally ruled out the presence of any active pulmonary lesions.

In the remaining series of 3,169 photofluorograms, all readers together noted 324 follow-up cases. The readers' personal results varied between 70 and 210 positive findings. Only 33 findings were evaluated identically as follow-up cases by all interpreters. As before, the readers differed in principle with regard both to their rates of detected follow-up cases and to their results in reading of the general material. This consistent disparity apparently suggested the probability that some interpreters accepted only conspicuous pulmonary lesions as follow-up cases.

The individual results prompt the following comments and *conclusions on single reading of photofluorographic series*. A greatly varying loss of significant findings has to be reckoned with, and its magnitude will depend on the reader's personal qualities such as his perspicacity, alertness, clinical judgment, experience, etc. The inter-individual variability evidently applies to all classified types of pulmonary lesions, but seems to be least in far advanced and greatest in minimal lesions. The likelihood of missed diagnoses, even in optimal single reading, therefore seems to be greatest for minimal, though active, pulmonary lesions.

In repeated mass surveys of the same population at relatively short intervals, most of the newly detected active lesions may be expected to be comparatively small ones. In photofluorogram interpretation, attention should accordingly be focussed more on the possible significance of minimal lesions, since they may often be incipient manifestations of various pulmonary diseases. The significance of initial tuberculous foci has been amply demonstrated by the detailed investigations of MALMROS & HEDVALL (1938).—In the present investigation the majority—65 per cent—of the test cases were minimal pulmonary lesions, and between 26 and 80 per cent of them had been overlooked at single reading. With this in mind, it cannot be ruled out that such changes might even be missed, within the limits of the same inter-individual variation, in single reading of other photofluorographic series. Since, moreover, not even larger active pulmonary lesions appeared to be evaluated uniformly and adequately, single reading must be considered in-

sufficient, associated as it is with too great a risk of subjective misinterpretations.

The magnitude of the observer error may evidently vary considerably in different interpreters, though it seems to be relatively constant in any single one; for here the results differed in more or less the same way regardless of whether they concerned the general material, NIELSEN's artefacts, or the test findings in this investigation.

In table 33 is presented the grading of the various readers in all three photofluorographic series and with respect to the intra-individual variation investigated here as well as in NIELSEN's investigation. There is manifestly a remarkable agreement between these gradings. This is especially evident if only those readers are studied who participated in all four investigations except that of the intra-individual variation, which latter is excluded because only five of the readers are represented.

In the two investigations which are of prime importance in this connection—*viz.* the general photofluorographic material comprising more than two million photofluorograms and the test photofluorograms with verified clinical diagnoses—the grading of the seven readers is identical. Furthermore, in another investigation performed with quite a different technique, i.e., NIELSEN's, the grading is again largely identical; it differs only in three readers. It is also interesting to note that the three highest scoring readers retain exactly the same grading in all instances.

For the purpose of minimizing the subjective error in single reading, *dual reading of photofluorograms* has been recommended as a safety measure (GARLAND, 1950; YERUSHALMY *et al.*, 1950; WEGELIUS, 1955). There are various ways of applying the method: an interpreter can make a second reading of his own initial results; two interpreters can read the same series either concurrently or independently, or they can check each other's initial results.

In the present test the readers checked to some extent their own evaluations as first or second interpreters at the original readings of the test photofluorograms 1–2 years earlier, and also in the capacity of first and second readers during the test. Since the test cases had originally been evaluated by one or other of the interpreters during the mass chest examinations of 1955–1956, similar results could be expected of them in the test. Yet on average only 68 per cent of these photofluorograms were once more noted as follow-up cases. As regards the *intra-individual variability,* the personal rates of identical evaluations of these cases ranged from 33 to 100 per cent (see table 25).—A similar intra-individual variability was found during the test, for the interpreters, in dual reading of each other's known initial results, corrected on only 424, or 74.8 per cent, of the 567 occasions in accordance with their personal initial findings (see table 23).

Table 33. Comparison of readers' grading in different investigations.

Grading according to				
General photofluorographic material (initial under-diagnosis)	Remaining test material (initial under-diagnosis)	Test photofluorograms (adequate interpretation)	Intra-individual variation (identical evaluation)	Nielsen's test (positive findings)
A. *All readers concerned*				
1	1	1		1
2				
3	3	2	1	4
4	2	3		2
5				
6				
7				
8	4	4		3
9	5	5	2	5
10	6	8	4	
11	7	6	3	7
12				6
13	8	7	4	8
14				9
B. *Only readers participating in all investigations except that of the intra-individual variation*				
1	1	1		1
2	3	2		4
3	2	3		2
4	4	4		3
5	5	5		5
6	6	6		6
7	7	7		7

In view of this great intra-individual variability in interpretation of the same photofluorograms at different times, the probability of a major diagnostic gain by checking of personal results seems open to question. This method accordingly appears unsuitable, its potentialities being limited, moreover, by the subjectivity of the single reader.

The *dual reading* methods treated in this paper consisted of independent dual reading and checking of known initial results. On *independent dual reading* by the various pseudoteams in the test, an average of 76.6 per cent of the test photofluorograms were regarded as follow-up cases. The average result was found to be about 15 per cent higher than in single reading. The pseudoteams' results ranged from 50 to 87 adequate evaluations among the total of 99 test cases. Misinterpretations in independent dual reading thus affected between 12 and 49 per cent of the test cases. The number of adequate evaluations made by a pseudoteam was, on the whole, dependent on the superior results of one member. In some two-man combinations the second reader did not contribute to the joint result (see table 17). The possibilities of more efficient evaluation of test photofluorograms were apparently limited, therefore, by the joint observer errors of the respective pairs. (Pseudoteams evaluated maximally 87, or 88 per cent, of the test photofluorograms as follow-up cases, and thus missed 12 per cent.)

The *limitations of independent dual reading through the joint observer errors* were also evident on analysis of the results when the pulmonary lesions had been grouped in accordance with the N.T.A. classification. Not even in far advanced lesions was a fully adequate evaluation accomplished by all pseudoteams (see page 53).—Of the 30 test photofluorograms with moderately advanced lesions, 13 per cent more, on the average, were evaluated as follow-up cases on independent dual reading than on single reading.—The superiority of dual reading was also evident from the interpretation of 65 minimal pulmonary lesions, for here an average of 43.5, or 66.9 per cent, of them were regarded as follow-up cases. This result was about 9.8 per cent higher than the corresponding figure for single reading. The pseudoteams overlooked or misinterpreted between 11 and 39, or 16.9–60 per cent of the test cases with active minimal pulmonary lesions. Thus the results obtained by the different pairs of readers varied considerably, and here too the superior initial results of one member could not be implemented by additional findings of the other. —In these circumstances overlooking or misinterpretation of a substantial number of clinically significant cases must even be expected in independent dual reading of other photofluorographic series, though most of these cases may be minimal pulmonary lesions.

Checking of known initial results in the test showed a reciprocal implementation of positive findings equal to that in independent dual reading; for, on the average, 75.9 of the test photofluorograms were regarded by the forty

pairs as follow-up cases (see table 23). On independent dual reading the same forty pairs interpreted adequately 75.8 of the test photofluorograms. The difference between the highest and lowest results was somewhat greater, however, when known initial results were checked (range 43–87 test cases). In general the numbers of positive findings which the readers, acting as checkers, added to the initial results were dependent on their original personal evaluations of the test cases; i.e., low scoring readers corrected high scoring ones to a lesser extent, and vice versa (see table 23). The interpreters showed, during the test, approximately the same grading as that in checking of each other's initial results after interpretation of the general photofluorographic material(*cf.* tables 9 and 27).

In the test it was possible to find out how many, and which, overlooked test cases the second reader corrected out of those that he himself, acting as first reader, had noted as follow-up cases. Such corrections in agreement with the interpreters' own initial diagnoses amounted to only 74.8 per cent of 567 instances. On checking known initial results, the second readers thus failed in every fourth case to correct in accordance with their own original evaluations; rather, one out of every four additional findings concerned a test photofluorogram which the checking interpreter had overlooked in his capacity of initial reader. Thus the intra-individual variability served to even out the misinterpretation of test cases on second reading, so that the results were brought up to the level of those after independent dual reading.

It emerged that 10 test cases were overlooked on single reading of the test series by all eight interpreters (see table 12). After 48 readings there still remained a further five test cases that had not been observed. Those missed on checking of known initial results by 40 two-man combinations were nos. 4, 6, 14, 48 and 52, all of which had active minimal pulmonary lesions. It is remarkable that since these cases had been detected 1–2 years earlier at interpretation of the general material, they were missed in all test readings, both by those who had originally detected them and by the others. From this it may be concluded that some active pulmonary lesions may even be overlooked in multiple interpretation of other photofluorographic series by one or more readers.

The primary aim of the test was to investigate the dependability of multiple evaluation of photofluorograms with respect to known positive findings. The procedure thus afforded no possibilities of elucidating the over-diagnosis rates. In the test it was found, furthermore, that second readers did not even correct initially "over-diagnosed" findings in the remaining test material. It is probable, therefore, that over-diagnoses rose after the checking of known initial results: The number of follow-up cases increased from 324 after eight readings to 520 after 48 readings.

The results indicated that the two dual reading methods were equal for

adequate evaluation of the test cases. Their effectiveness was evidently limited to the same extent by the joint observer errors of the respective pairs of readers, which could vary substantially. The procedure in independent dual reading calls for a much bigger staff and far greater financial resources than second reading of known initial results, without being superior thereto. Under these circumstances it would appear that the method employed is immaterial as long as all readers do not have uniform standards of evaluation and the magnitude of the observer error in a team is unknown.

The present investigation disclosed a relatively poor degree of concordance in the readers' evaluations of test cases. It followed that different interpreters held different views on the significance of various pathologic photofluorographic findings and their need of further examination. This explains why the readers found varying numbers of follow-up cases in the same series.—In the interpretation of survey films the aim must be to observe all pathologic changes, in order to ensure follow-up examination of the greatest possible number of clinically significant cases. At the same time the material must be so sifted as to obviate follow-up examinations of insignificant findings as well as misinterpretation of significant ones. In his endeavours to differentiate such findings, the interpreter is confronted with a responsible and problematic task, for his diagnoses should be as concordant as is feasible with the subsequent clinical findings. The norms for differentiation of pathologic findings that require follow-up examination from those which experience shows to have no significance, should be as uniform as possible for all interpreters and should be adapted to the preventive aspects and aims of mass examinations.

In photofluorogram interpretation a distinction must be made between two factors: Observation of a lesion and evaluation of its significance. The detection of pathologic changes calls not only for a knowledge of the normal conditions, but for perception and alertness, while the evaluation requires sound clinical judgment, experience and some degree of intuition. A reader may be wanting in the ability to perceive or to evaluate abnormal photofluorographic findings. Inter-individual differences in this respect have been the subject of some investigations, which have led to measures designed, by *training of readers,* to secure a standardization of norms for interpretation (Brodeur, 1954; Nielsen, 1955). Yet it also seems necessary, after such training, to find out if a reader applies the same norms in practice, or in which respects his evaluations differ from those of his colleagues. For this purpose, testing seems appropriate.

The present investigation has shown that *testing* with a suitable photofluorographic series will yield useful information on an interpreter's qualities and subjective observer error, besides revealing the types of pulmonary lesions that are most commonly misinterpreted. A test may show, furthermore, the

degree to which the results are improved by cooperation between several readers; and it will indicate, too, the probable magnitude of the observer error in different forms of single or multiple interpretation.

If all readers were equally efficient, then dual reading might well appear to be unnecessary. However, various psychologic factors, fatigue, etc. may, even if temporary, influence a reader's concentration during the work itself. Dual reading may do much to reduce such sources of error, while at the same time the effectiveness and reliability of photofluorographic diagnosis can be maintained at a more constant level.

The study reported here, and the conclusions that have been drawn, are based on local conditions and they throw light on a problem the importance of which may vary in different places. The main purpose of the investigation was to elucidate the significance of the human factor in photofluorogram reading, and the possibilities of counteracting that source of error. For this purpose it was necessary to analyze the error in the personal diagnosis, in order to estimate the potential errors associated with multiple interpretation of photofluorograms.

Summary

The investigation reported here was designed to elucidate the significance of the observer error in single and multiple reading of photofluorograms. It was prompted by the inconsistent results of dual reading, by fourteen interpreters, of 2,084,583 photofluorograms from mass chest examinations in Sweden; for this variability pointed to inter-individual differences in the approach to evaluation of pathologic findings.

Eight of the fourteen readers interpreted, for the purposes of this study, a series of 3,268 photofluorograms among which were dispersed 99 test cases with clinically verified active pulmonary lesions. This test material was first read independently, after which the interpreters checked each other's known initial results. On single reading, an average of 61 per cent of the test cases were evaluated adequately as follow-up cases; the personal under-diagnosis rates varied between 18 and 73 per cent of the test cases. Some points of agreement were found with the readers' under-diagnosis rates that had emerged from the reciprocal correction of findings in dual reading of the general photofluorographic material. Analysis of the results after independent dual reading of the test cases and after the interpreters' checks of each other's known initial results, showed that evaluations concording with the clinical diagnoses averaged 76 per cent of the test cases. Just as the superiority of dual to single reading was evident, so was the significance demonstrated of the observer error in multiple interpretation of photofluorograms. The dependability and effectiveness of dual reading varied with the joint observer error of different pairs of readers.

Aside from the inter-individual difference, the significance was investigated of intra-individual variability in the evaluation of the same photofluorograms at different times. On comparison of original evaluations with those of the same positive photofluorograms after an interval of 1–2 years, the interpretations were found to vary by an average of 32 per cent.

As a measure to increase the effectiveness of photofluorographic diagnosis, training of interpreters is recommended with a view to securing common standards of evaluation. The results of this investigation suggest, moreover, that even testing of interpreters is advisable, to elucidate their subjective observer errors and their suitability for photofluorogram reading; for on this basis the reliability of dual reading should be enhanced.

Key to Case Histories of Test Photofluorograms

Case No.	Photofluorogram No.	Dispensary Journal No.	Sex	Age Years	Clinical Diagnosis
1	A. 13078/34	560688 561015	♀	17	Tuberculosis, right lung
2	L. 5045/12	560528 560788	♀	18	Tuberculosis, left apex
3	R. 20508/38	561144 561320	♀	23	Bilat. apical tuberculosis
4	L. 28301/89	540839 541203	♀	24	Tuberculosis, left apex
5	E. 7863/90	520043 511978	♀	24	Tuberculosis, left lung
6	J. 31797/91	560849 501381	♀	25	Carcinoma, right lung
7	L. 1026/29	560414 560317	♀	26	Bilat. apical tuberculosis
8	J. 9224/14	560653 560736	♀	26	Tuberculosis, left apex
9	D. 24847/36	570030 561480	♀	26	Tuberculosis, right apex
10	J. 31158/62	550952 550953	♀	27	Tuberculosis, right apex
11	L. 48980/8	570022 561677	♀	28	Tuberculosis, right apex
12	A. 33160/9	561165 301979	♀	30	Tuberculosis, right apex
13	A. 43253/10	570101 570123	♀	31	Tuberculosis, left lung
14	J. 30889/92	530136 530109	♀	31	Tuberculosis, left apex
15	V. 31616/93	480473 480543	♀	33	Tuberculosis, right lung
16	J. 30819/57	560634 440201	♀	35	Tuberculosis, left apex
17	T. 10162/94	514178 500908	♀	35	Tuberculosis, right lung
18	A. 1520/35	560518 560255	♀	35	Tuberculosis, right apex
19	A. 22030/32	560829 461022	♀	35	Tuberculosis, right apex
20	A. 18089/15	560547 560794	♀	35	Tuberculosis, right lung
21	J. 31870/95	480744 482163	♀	36	Tuberculosis, right lung

Case No.	Photofluorogram No.	Dispensary Journal No.	Sex	Age Years	Clinical Diagnosis
22	A. 18234/58	560299 551353	♀	38	Tuberculosis, right lung
23	L. 48181/96	510441 510244	♀	38	Tuberculosis, left lung
24	A. 7229/16	560129 560485	♀	41	Tuberculosis, left lung
25	A. 8561/59	560122 560184	♀	44	Tuberculosis, left apex
26	V. 26470/97	472736 462685	♀	44	Bilat. tuberculosis
27	A. 6049/30	560772 560414	♀	45	Bilat. tuberculosis
28	F. 26097/11	8 561413	♀	46	Tuberculosis, left lung
29	F. 33806/39	570233 570287	♀	46	Tuberculosis, right lung
30	A. 697/60	561058 550438	♀	47	Tuberculosis, right lung
31	R. 24152/42	570085 561510	♀	49	Tuberculosis, left lung
32	M. 7282/46	— 46 D 5	♀	50	Tuberculosis, right apex
33	L. 44357/98	510615 510865	♀	52	Tuberculosis, right lung
34	A. 39172/40	— 452221	♀	56	Bilat. tuberculosis
35	O. 43574/65	— 551310	♀	57	Carcinoma, right lung
36	E. 16476/63	560989 551436	♀	57	Tuberculosis, right apex
37	A. 10770/31	560588 560888	♀	59	Tuberculosis, left lung
38	A. 6625/33	— 560415	♀	62	Tuberculosis, right lung
39	A. 32013/41	561160 160788	♀	62	Bilat. tuberculosis
40	A. 16703/66	— 551365	♀	63	Metastasis, right lung
41	F. 26541/37	570195 561649	♀	66	Tuberculosis, left lung
42	A. 2164/17	560624 560259	♀	66	Tuberculosis, right lung
43	L. 29050/67	— 550975	♀	70	Carcinoma, left lung
44	E. 12926/61	551050 391235	♀	71	Tuberculosis, left apex

Case No.	Photofluoro-gram No.	Dispensary Journal No.	Sex	Age Years	Clinical Diagnosis
45	J. 16376/3	— 571188	♀	71	Tuberculosis, left lung
46	D. 28651/5	561183 561618	♂	16	Bilat. tuberculosis
47	T. 4466/77	8 550249	♂	20	Tuberculosis, right apex
48	T. 13944/78	520032 520021	♂	22	Tuberculosis, right apex
49	T. 3095/48	550390 551422	♂	23	Tuberculosis, right apex
50	A. 1021/18	560360 560269	♂	25	Tuberculosis, right apex
51	G. 30926/79	530605 530752	♂	25	Tuberculosis, left lung
52	V. 27311/80	490656 490688	♂	26	Tuberculosis, left lung
53	A. 29422/6	561175 561676	♂	27	Tuberculosis, right apex
54	L. 33786/81	530803 500534	♂	30	Tuberculosis, left lung
55	A. 10690/19	560850 561181	♂	31	Tuberculosis, right lung
56	O. 38106/49	560076 560120	♂	33	Tuberculosis, right lung
57	L. 34886/82	530156 530164	♂	31	Tuberculosis, left lung
58	L. 20043/20	560824 560787	♂	34	Tuberculosis, right apex
59	J. 18303/47	— 57 D 5	♂	38	Tuberculosis, left lung
60	R. 16711/7	561135 561270	♂	38	Tuberculosis, left lung
61	J. 31689/83	— 370130	♂	38	Tuberculosis, right lung
62	E. 9846/68	— 55 D 1	♂	38	Mediastinal cyst
63	O. 46394/50	560306 560239	♂	39	Tuberculosis, right lung
64	Z. 21792/4	— 561257	♂	41	Tuberculosis, left apex
65	A. 9087/21	561025 560518	♂	43	Tuberculosis, right lung
66	A. 23686/51	551121 551378	♂	44	Tuberculosis, right apex
67	A. 14251/84	501114 341722	♂	45	Tuberculosis, right lung

Case No.	Photofluorogram No.	Dispensary Journal No.	Sex	Age Years	Clinical Diagnosis
68	O. 32305/99	560236 551092	♂	45	Tuberculoma, right lung
69	V. 34020/85	560202 551130	♂	46	Tuberculosis, left lung
70	L. 25090/22	560669 561003	♂	48	Tuberculosis, right lung
71	T. 15005/86	540337 540771	♂	48	Tuberculosis, right lung
72	V. 33360/52	561126 561630	♂	49	Tuberculosis, right lung
73	O. 2981/23	560245 560303	♂	50	Tuberculosis, right lung
74	V. 21968/53	8 551123	♂	51	Tuberculosis, right lung
75	A. 14488/54	560043 560056	♂	51	Tuberculosis, left apex
76	V. 535/24	560369 560320	♂	51	Bilat. apical tuberculosis
77	L. 39598/69	— 55 D 7	♂	52	Carcinoma, right lung
78	L. 27653/25	560884 561027	♂	52	Tuberculosis, right lung
79	A. 16202/87	540923 541111	♂	55	Bilat. apical tuberculosis
80	A. 3168/100	— 560220	♂	57	Silicosis
81	O. 7630/26	560461 470317	♂	57	Tuberculosis, right lung
82	O. 41840/88	501311 550512	♂	58	Tuberculosis, left lung
83	L. 48329/55	560149 560064	♂	59	Tuberculosis, left lung
84	R. 25035/2	— 492270	♂	60	Carcinoma, left lung
85	V. 39863/56	530363 560536	♂	60	Tuberculosis, left lung
86	T. 15042/70	— 550707	♂	62	Carcinoma, right lung
87	T. 7048/71	— 55 D 4	♂	63	Carcinoma, right lung
88	V. 33864/72	560192 560093	♂	63	Metastasis, right lung
89	O. 39838/73	— 55 D 4	♂	65	Carcinoma, right lung
90	F. 35012/44	570073 570396	♂	65	Tuberculosis, right lung

Case No.	Photofluorogram No.	Dispensary Journal No.	Sex	Age Years	Clinical Diagnosis
91	T. 13919/74	— 550682	♂	66	Carcinoma, right lung
92	A. 19472/27	560595 560837	♂	66	Bilat. tuberculosis
93	E. 11120/45	— SSfu 2	♂	69	Metastasis, right lung
94	T. 9526/75	— 550596	♂	70	Carcinoma, right lung
95	L. 10920/28	560333 560475	♂	71	Bilateral tuberculosis
96	L. 10110/1	— 560470	♂	80	Carcinoma, left lung
97	V. 39887/76	— 56 D 4	♂	79	Carcinoma, left lung
98	E. 15697/64	550838 550660	♂	76	Tuberculosis, left lung
99	F. 27108/43	— 561714	♂	81	Tuberculosis, left lung

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TUBERCULIN
REACTIONS
IN DOGS

FROM THE INSTITUTE OF INTERNAL MEDICINE OF
THE VETERINARY COLLEGE NORWAY, OSLO
(Head: Professor Johs. L. Flatla)

TUBERCULIN REACTIONS IN DOGS

BY

OLAV ASBJØRN BERG

EJNAR MUNKSGAARD

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Preface

The investigations here presented were carried out at the Small Animal Clinic, Institute of Internal Medicine, the Veterinary College of Norway, in the years 1949—55.

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I am also indebted to Professor dr. med. vetr. R. Svenkerud for furnishing the tuberculins used, to the late Professor A. J. Brandt for having performed the bacteriological and post mortem examinations of the dogs in the 1st series of experiments, and to Prosektor S. Erichsen for carrying out the post mortem examinations of the dogs in series No. 2.

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Oslo, May 1957.

Olav Asbjørn Berg.

A. Introduction

Koch's hope that the tuberculin might be used therapeutically soon had to be given up. But on the other hand it proved to be valuable as a diagnostic means in tuberculosis. In the same year as it was launched (1890), *Guttmann* tried it diagnostically on animals (cited after *Holth,* 1923). Both in human and in veterinary medicine the tuberculin reaction is still the most important test as to whether an indvidual has been affected by tubercle bacteria.

Both the tuberculin itself and the methods of testing have been made the subjects of constant investigations, and up to the present time opinions have been divided as to which procedure gives the most reliable result.

The uncertainty that has been felt may probably be ascribed to the fact that hitherto sufficiently exact methods of standardizing have been missing. As to Old Tuberculin, (O. T.) which has chiefly been applied until quite recently, the standardizing is done by biological methods. As a common denominator (International Standard Tuberculin) a special English Old Tuberculin, deposited in Denmark, has been used.

With the introduction of a purely synthetic medium into the production of tuberculin one can profitably undertake a determination of the content of protein as a supplement to the biological standardizing. An essential advantage of heat concentrated synthetic medium tuberculin (HCSM) as well as of the Purified Protein Derivative (P.P.D.) — should be the the fact that in comparison with Old Tuberculin it has a less irritative, non-specific effect, as it shows full potency in tuberculin positive animals. This is of a special importance in animals with a faint allergy. *(Buxton & Glover, 1939).*

The outcome of a tuberculin test should give a decisive response as to whether there is a tuberculous infection or not. This ideal demand can hardly be expected to be 100 per cent satisfactory in such a biological test. We have at any rate not yet arrived so far. Studies of literature lead up to the conception that a certain hesi-

tancy is still prevailing. Characteristic of the situation, perhaps, is a pronouncement by *Nissen Meyer* (1951), saying that for no known tuberculin reaction may a limit value be fixed which quite reliably distinguishes tuberculously infected from non-infected individuals.

The problem may be said to have been further complicated by the introduction of the BCG vaccination. It is true that the question of discriminating between vaccination allergy and allergy as a consequence of infection with virulent bacteria has been studied (*Hertzberg* 1949), but the problem can hardly be considered to be finally solved.

The different modes of application that have been tried may be put into 2 main groups: a general reaction to subcutaneous or intravenous injection; and a local reaction to application to or in the skin or mucous membranes is registered.

Generally, tuberculin tests are considered to be less reliable in carnivora (and other non-ruminants) than in cattle and man (*Feldman*, 1934, *Glover*, 1949, *Freudiger*, 1956). One is particularly sceptical as to the value of such tests in dogs. When studying the literature on this subject, one gets the impression that there is a considerable difference of opinion as to the value of tuberculin tests in dog in general, as well as to which method is to be preferred (see *Inchaurreguy & Blasi*, 1910 (ophthalmic (ophth.), cutaneous ad mod. v. Pirquet (Pirquet)), *Cobbett & Griffith*, 1913 (subcutaneous (s.c.)), *Zwick & Titze*, 1913 (s.c.), *Eber*, 1917 (p. 231) (s. c.), *Verge*, 1923 (s.c.), *Lesbouyries*, 1926 (s.c., ophth., Pirquet, intracutaneous ad mod. Mantoux (Mantoux), epicutaneous), *Stableforth*, 1929 (s.c.), *Gerlach*, 1931 (s.c., ophth, Mantoux), *Mills & Colwell*, 1937 (s.c., Mantoux), *Hutyra et al.*, 1938, p. 634 (s.c.), *v. Goidsenhoven & Schoenaers*, 1939 (s.c., Mantoux), *Lovell & White*, 1940 (s.c.), *Colwell & Mills*, 1940, a & b (Mantoux), *Lasserre et al.*, 1941 (s.c., ophth., Mantoux, intravenous (i.v.)), *Gunn, Sheehy, Colwell & Mills*, 1942 (Mantoux), *Gunn, Mills, Shepard & Barth*, 1943 (Mantoux), *Moltzen-Nielsen & Plum*, 1943 (s.c., Mantoux), *Teunissen*, 1948 (s.c., ophth., Pirquet), *Builder*, 1948 (s.c.), *Urwitz*, 1949 (s.c., Mantoux), *Ukrainczyk-Laborie & Laborie*, 1952 (i.v.), *Freudiger*, 1956 (s.c., Mantoux, ophth.)). Especially concerning the intracutaneous test ad modum Mantoux, the results of Colwell, Gunn and Mills et al. (l. c.) with O.T. as well as P.P.D. indicate a very high degree of reliability (more than 90 per cent positive reactions in experimentally infected dogs). *Francis* (1956), however, has found that intradermal tests with PPD are not dependable in dogs.

Urwitz, 1949, states that the best method of diagnosing tuberculosis in dog as well as in man is radiographic examination of the lungs. Yet it is difficult to accept this contention, because tuberculosis in dogs occurs rather frequently without the lungs being involved. Therefore it is not very probable that tuberculosis in dogs as a clinical diagnostic problem could be solved by means of radiographs only. The clinician first and foremost has to depend on the allergic tests besides the clinical and bacteriological examinations.

With this background it must be considered desirable to obtain further information of tuberculin tests in dog.

This study is a report of personal investigation on the intracutaneous application of tuberculin on the thorax.

B. Own investigations

I. OLD TUBERCULIN

Three kinds of Old Tuberculin were used. Most tests were done with ordinary Norwegian O.T. (produced ad modum Holth) — from now on called tuberculin V — from the State Veterinary Institute, Oslo. Another Norwegian tuberculin, produced by Svenkerud, Oslo, (hereafter called tuberculin F) also was used, along with Danish standardized tuberculin from the State Serum Institute, Copenhagen (hereafter called tuberculin D). The potency of these tuberculins was originally stated to be 1.4, 2.4, and 1.7 times as potent as the international standard. After the present work had been concluded, *Svenkerud,* however, has stated quite other potencies. According to him, tuberculin F has the same potency as the International Standard Tuberculin, of which 0.01 mg corresponds to 1 I.U. Tuberculin D is only half as strong (50 per cent), and tuberculin V has a potency of only 30 per cent in relation to the International Standard Tuberculin (personal information).

The tests were done and read as they usually are in cattle: After cutting the hairs close with scissors, the thickness of the folded skin was measured with cutimeter (a sliding gauge graduated in millimeters), and 0.1 ml of tuberculin was injected intracutaneously, making a distinctly visible and palpable prominence on the surface of the skin. The measuring of the skin fold was then repeated after 24,48 and 72 hours.

The volume injected always was 0.1 ml. The amount of tuberculin varied from 750 to 5,000 I.U. Most tests were done with 50 per cent of tuberculin V, corresponding to 1,500 I.U. (in 0.1 ml of volume).

The injections were made laterally on the thorax behind the shoulder, partly in the middle (T), partly high dorsally (DT), partly far ventrally (VT).

In all readings the principle has been followed that the measuring forms for previous measurings have not been looked over till the day's measurings have been recorded, to preclude prejudicial influences regarding the readings. The subjective error of mea-

suring on the whole kept at 0-0.5 mm. If the evaluation of the skin measurements could be based upon the same limit of specific positive reaction in dog as in cattle (3 mm of increase, cf. *Plum,* 1937), the exactness should be sufficiently great. If, however, the limit of specific reaction should be considerably lower in dog (an increase of 1 mm has been assessed positive by *Moltzen-Nielsen & Plum,* 1943), it would seem difficult to assess the skin reaction by the method described.

The relative increase of the skin thickness has also been used as a mode of assessment. For cattle the demand for positive reaction sets a limit of at least 50 per cent increase (*Hutyra et al.,* 1938, p. 642). But here the variations of the normal thickness of the skin before the injection enter as a determining factor, and such variations are considerable, even in the same skin region of the individual dog (Table No. 1). In 383 measurings in 85 dogs of different breeds and age and of either sex, the skin fold thickness laterally on the thorax averaged 6.0 mm (2—12) dorsally (DT) (99 observations in 14 dogs), 4.5 mm (2—9.5) in the middle (T) (232 observations in 74 dogs), and 3.1 mm (2—5) ventrally (VT) (52 observations in 7 dogs).

Besides the measurings of the absolute (mm) and the relative (per cent) increase in skin fold thickness, visible and palpable changes of the skin (rubor, tumor, calor, dolor) should also be noted and taken into consideration in the assessment. However, in dog very often only tumor (oedema) is found. Rubor will not easily be recorded because the skin is often pigmented.

Table No. 1.

Pre-injection skin fold measures laterally on the thorax, mm. Mean values and limits of variation observed in 7 litter mates. No. of observations in each dog: 11 dorsally and 8 ventrally.

Dog No.	Dorsally (DT)	Ventrally (VT)
1/50	5.3 (2.5—7.0)	3.0 (2.5—3.5)
2/50	4.9 (2.0—7.0)	2.9 (2.0—4.0)
3/50	4.8 (2.0—6.5)	2.7 (2.0—3.0)
4/50	6.2 (3.0—10.0)	3.8 (3.0—4.5)
5/50	4.6 (2.5—6.0)	2.8 (2.0—5.0)
6/50	5.0 (3.0—6.5)	3.4 (3.0—4.0)
7/50	5.1 (2.5—6.5)	3.2 (2.5—4.0)

1. Experimental dogs.

A litter of 8 German shepherd dogs were born and reared in isolation from other animals and otherwise in conditions which would mean no danger of spontaneous infection with tubercle bacteria (tbc.) from persons, food, etc.

At the age of 6 months, 5 of the dogs were inoculated with BCG vaccine, produced at the Norwegian BCG Laboratory, Bergen (cf. *Berg*, 1954). Later all 8 dogs were inoculated with virulent tbc. of the typus humanus, the first inoculation being performed 225 days after BCG vaccination. As infection material an approximately 8 weeks old culture of the tbc. on Loewenstein's medium (A. J. Brandt's strain "M. H. 193") was used. Further data on dosis and mode of infection, time of observation and post mortem findings appear in Table No. 2.

Infection in 3 normal dogs (Nos. 1/50, 7/50, 8/50).

0.01 mg of tbc. injected subcutaneously on the neck did not give rise to any clinical symptoms or postmortal changes in the course of 85 days, and tbc. could not be detected (dog No. 8/50).

1 mg of tbc. subcutaneously on the neck produced during 44 days a complete primary complex in the site of infection and the regional lymph nodes with a slight tendency to spreading (to the lungs). Tbc. were cultivated from the primary lesions, but not from the lungs or urine (dog No. 1/50).

c. 40 mg of tbc. perorally (with stomach tube) did not produce any clinical symptoms in 225 days, and tbc. could not be detected in the urine. Post mortem. however, tuberculous tissue and tbc. were found in the mesenteric lymph nodes (dog No. 7/50).

These results confirm earlier experiences (cf. *Cobbett*, 1907, *Chaussé*, 1910, *Schrum*, 1910, *Eber*, 1917, *Lasserre et al.*, 1941), which indicate that dog has a relatively high natural resistance to experimental infection with tbc. perorally or subcutaneously.

Infection in 5 dogs, 225—369 days after BCG vaccination.

3 dogs (Nos. 2/50, 4/50, 6/50) were inoculated with increasing doses of tbc., twice subcutaneously (0.01 mg and 1 mg) and once perorally (30 mg) during 144 days. During the time of observation

(226—237 days after the initial inoculation with tbc.) none of the dogs showed any signs of general discomfort. Local reactions were produced only after the second subcutaneous infection, forming small processes, from which tbc. of the typus humanus were isolated. The exudative inflammations subsided in a couple of months in all 3 dogs. Post mortem tuberculous processes or tbc. could not be detected.

In 2 dogs (Nos. 3/50, 5/50), c. 40 mg of tbc. perorally did not produce clinical symptoms or postmortal changes in 236 and 230 days, and tbc. could not be detected post mortem.

The post mortem and bacteriological examinations were performed by the late professor A. J. Brandt.

Table No. 2.

Experimental Infection. Series No. 1.

Dog No.	Inoculations				Exudate[1]) 5/18/51	Days of[2]) obs.	Weight differ. kg[3])	Post mortem		
	BCG, mg. 6/20/50	virulent tbc., mg						Aut[4])	Hist[5])	Cult[6])
		2/1/51	4/28/51	6/26/51						
8/50		0.01 s				85	+ 0.5	0	0	0
1/50			1 s		+	44	+ 0.7	+	+	+
7/50		0.1 p	10 p	30 p		225	÷ 1.7	0	+	+
3/50	0.1 i	0.1 p	10 p	30 p		236	÷ 0.4	0	0	0
5/50	1 i	0.1 p	10 p	30 p		230	+ 1.5	0	0	0
2/50	0.1 i	0.01 s	1 s	30 p	+	237	+ 0.5	0	0	0
4/50	1 i	0.01 s	1 s	30 p	+	233	+ 0.8	0	0	0
6/50	1 i and 1 s	0.01 s	1 s	30 p	+	226	÷ 0.3	0	0	0

1) Exudate from fistulae at the site of infection, examined for tbc.
2) No. of days from the first inoculation with virulent tbc. to the day of euthanasia.
3) Difference in body weight on the day before the first infection and on the day of euthanasia.
4) Macroscopic tuberculous lesions.
5) Microscopic tuberculous lesions.
6) Growth on Loewenstein's medium.

+: tuberculous lesions or tbc. found
0: tuberculous lesions or tbc. not found
i: intracutaneously, s: subcutaneously, p: perorally

Table No. 3.

Maximum reaction after intracutaneous injection of 0,1 ml of Old Tuberculin on the thorax.

Experimental dogs. Series No. 1.

Dog No.	Date	Cond.	750-1,000 I.U.-Type V and F[1])				1,500 I. U.-Type V				5,000 I. U.-Type D and F[2])			
			Skin fold measure			P. M.	Skin fold measure			P.M.	Skin fold measure			P.M.
			before inj.	max. increase mm	max. increase p. c.		before inj.	max. increase mm	max. increase p. c.		before inj.	max increase mm	max increase p. c.	
1/50	4. May 1950	N					4	2	50	72				
	19. Sept. 1950	»					4.5	2	44	24				
	28. Nov. 1950	»	5	1.5	30	72					5.5	2	36^{ex}	48
	5. Apr. 1951	»					6.5	1.5	23	24-72	6.5	1	15	72
	29. May 1951	I	2.5	3	120	48	2.5	3	120	24-72	2.5	3	120	48
2/50	4. May 1950	N					4.5	1	22	24				
	19. Sept. 1950	V					4	3	75^{oe}	24				
	28. Nov. 1950	»	5.5	1	18	24-72					5	3	60	72
	5. Apr. 1951	I					6.5	2.5	39	24	6.5	3.5	54	72
	29. May 1951	»	2	1.5	75	48	2	1.5	75	48-72	2	4	200	48-72
	5. Sept. 1951	»									F 3	1.5	50	24-72
	»	»	2.5	1	40	48	2.5	3	120	72	3	3.5	116^{ex}	72
3/50	4. May 1950	N					5	2	40	24-48				
	19. Sept. 1950	V					5	2	40	24				
	28. Nov. 1950	»	5.5	1	18	24-72					5.5	3.5	64	24
	5. Apr. 1951	I					6.5	1.5	23	48-72	6.5	3	46	48
	29. May 1951	»	2	1	50	48-72	2	1.5	75	48-72	2	2.5	125	48-72
	5. Sept. 1951	»									F 3	2	67	24-48
	»	»	2.5	1	40	24-72	3	2.5	83	48	3	2.5	83^{ex}	24-72
4/50	4. May 1950	N					5.5	1	18	72				
	19. Sept. 1950	V					4.5	2.5	55	24-48				
	28. Nov. 1950	»	7	1	14	48					6.5	3.5	54	72
	5. Apr. 1951	I					8.5	1	12	48-72	7	4.5	64^{ex}	48
	29. May 1951	»	3	2	67	48	3	2	67	48-72	3	4.5	150	48
	5. Sept. 1951	»									F 4	2.5	63	72
	»	»	4	0.5	13	24-72	4	3	75	24	4.5	4	89^{ex}	72

5/50	4. May 1950	N					5	1.5	30	72				
	19. Sept. 1950	V					2.5	2.5	100^{ex}	24				
	28. Nov. 1950	»	5	3	60	24					6	1.5	25	24-48
	5. Apr. 1951	I					5.5	1	18	48-72	5.5	3	55	48
	29. May 1951	»	2.5	2	80	24	2.5	0.5	20	24-72	2.5	3	120	24
	5. Sept. 1951	»									F 2	1.5	75	24
	»	»	2.5	1	40	24-72	2	2.5	125^{oe}	72	2.5	2	80	48-72
6/50	4. May 1950	N					4	1.5	38	24-48				
	19. Sept. 1950	V					6.5	3.5	54^{ex}	24				
	28. Nov. 1950	»	6	1.5	25	24					5	2.5	50	24-72
	5. Apr. 1951	I					5.5	2.5	46	48	5.5	4	73^{ex}	48
	29. May 1951	»	3	0.5	17	24	3	1.5	50	24	3	3	100	48
	5. Sept. 1951	»									F 3	2.5	83^{oe}	24
	»	»	4	1	25	24-72	3.5	2	57	48	3	3.5	116$^{oe}_{ex}$	72
7/50	4. May 1950	N					5	0.5	10	24-48				
	19. Sept. 1950	»					5.5	1	18	24-48				
	28. Nov. 1950	»	5.5	0	0	0					5	3	60^{oe}	24-72
	5. Apr. 1951	I					6.5	0.5	8	24-72	6.5	2.5	39^{ex}	24-72
	29. May 1951	»	2.5	1.5	60	24-48	2.5	1.5	60	48-72	2.5	3.5	140	48
	5. Sept. 1951	»									F 3	2	67	48
	»	»	3	2	67	24	3	2	67	24	3	2	67	24-72
8/50	4. May 1950	N					6.5	1	15	24				
	19. Sept. 1950	»					7	1	14	24				
	28. Nov. 1950	»	8	2.5	31	24^{oe}					8	2.5	31^{oe}	24
	5. Apr. 1951	I					7.5	1.5	20	48-72	7.5	5.5	73^{ex}	48

1) Type V used on the 28. Nov. 1950, type F on the 29. May 1951 and 5. Sept. 1951.

2) Type F used in 1 of the tests on the 5. Sept. 1951 (F).

N: Normal condition, V: BCG vaccinated, I: Infected with virulent tbc

mm: Absolute increase, p. c.: relative increase (per cent).

P.M.: No. of hours after injection, when maximum reaction was observed (punctum maximum).

er: erythema, oe: oedema, ex: exsudatio.

On the 29. May 1951 the dogs had been superinfected twice.

—»— 5. Sept. 1951 —»— —»— thrice.

Results (Table No. 3).

1,500 I.U. OF TUBERCULIN

Normal dogs.

In 12 tests on the 8 experimental dogs in normal condition a maximum increase in thickness of the skin of 0.5—2 mm (10—50 per cent) was observed. Assuming an erroneous subjective measure of maximum 0.5 mm or 20 per cent (relative measure), the limit of non-specific reaction in normal dogs might be set at 2.5 mm (60 per cent).

In 15 tests on 10 other normal dogs (where no disease or infection could be detected, see later) the maximum reaction was 0—2 mm (0—44 per cent) (Table No. 4, a). This agrees very well with the results in the normal experimental dogs.

BCG-vaccinated dogs.

In 1 dog (No. 2/50), which in normal condition showed a reaction of 1 mm (22 per cent), the reaction was c. 4½ months after intracutaneous injection of 0.1 mg of BCG vaccine 3 mm (75 per cent). In another dog which was given the same BCG dose (No. 3/50), the reaction was the same as before the vaccination, namely 2 mm (40 per cent). In 2 dogs, which were given 1 mg of BCG intracutaneously (Nos. 4/50 and 5/50), the reaction increased from 1 and 1.5 mm (18 and 30 per cent) to 2.5 mm (55 and 100 per cent). In 1 dog, which was given 1 mg of BCG intracutaneously and at the same time 1 mg subcutaneously (No 6/50), the reaction increased from 1.5 mm (38 per cent) to 3.5 mm (54 per cent).

Out of the 5 vaccinated dogs, then, 2 animals showed reactions which, both in relation to the reactions in the same dogs before the vaccination, and compared with simultaneous reactions in normal dogs of control, must be said to lie just outside the normal limits of variation (Nos. 2/50 and 6/50). In a third dog (No. 5/50) the post-vaccinal reaction was near the limit of non-specific reaction, judging by the absolute measure, but distinctly above this, when assessed by the relative increase (100 per cent). In the 2 last dogs the post-vaccinal reactions lay within the limit of normal variation, irrespective of the method of estimation.

Dogs infected with virulent tubercle bacteria.

Peroral infection.

In tests c. 10 months after BCG vaccination and c. 2 months after peroral ingestion of 0.1 mg of bacteria the reactions were less marked than 3 months after BCG vaccination in 2 dogs (Nos. 3/50 and 5/50). In the non-vaccinated one (No. 7/50) the reaction had to be assessed as altogether non-specific.

C. 4 weeks after peroral superinfection with c. 10 mg of bacteria (tests on the 29. May 1951) the reactions in all the 3 dogs were also non-specific, namely 0.5—1.5 mm (20—75 per cent).

After the dogs had been given in all c. 40 mg of virulent tubercle bacteria per os, c. 10 weeks later they still showed reactions which lay at the uppermost limit of non-specific reaction, namely 2—2.5 mm (65—125 per cent). In examination post mortem a short time after these tests, in 2 of the dogs no certain signs of tuberculous infection were found, whereas in the 3rd (No. 7/50) both living bacteria and small tuberculous processes were found.

Subcutaneous infection.

In the 2 non-vaccinated dogs it was found that 2 months after subcutaneous inoculation with 0.01 mg of bacteria the reaction was only 1.5 mm (20 per cent) (No. 8/50). Post mortem neither tubercle bacteria nor tuberculous processes were found in this dog. In the other dog (No. 1/50), about 4 weeks after subcutaneous infection with 1 mg of bacteria a reaction of 3 mm (120 per cent) was found. Post mortem 2 weeks later showed both living tubercle bacteria and tuberculous processes (primary complex).

In the 3 vaccinated dogs (Nos. 2/50, 4/50 and 6/50) it was found that about 10 months after vaccination and about 2 months after subcutaneous injection of 0.01 mg of virulent bacteria (tests on the 5. Apr. 1951) the reactions were within the normal range, even in the 2 dogs which c. 3 months after vaccination had shown a tendency to positive reaction. After an additional inoculation with c. 1 mg of bacteria subcutaneously there was still no distinctly positive reaction (tests on the 29. May 1951). When further 30 mg of bacteria had been given per os, tests about 10 weeks later (5. Sept.) showed that 2 of the dogs actually had reactions which might not be called non-specific, namely 3 mm (75—120 per cent), whereas the 3rd dog still reacted with 2 mm only (67 per cent). In examination post mortem

shortly after the last tuberculin test neither tuberculous processes nor tubercle bacteria were found in these dogs. But c. 3 weeks after the subcutaneous infection with virulent tubercle bacteria, virulent bacteria of the typus humanus were detected in the exudate from the site of inoculation in all 3 of them.

In 2 out of 3 dogs which after BCG vaccination had been superinfected both perorally and subcutaneously reactions were also found which might be called faintly positive (3 mm or 120 per cent). But, on the whole, intracutaneous injection of 1,500 I.U. of Old Tuberculin has not manifested any distinctly specific tuberculous allergy 10—15 months after BCG vaccination, nor after infection with up to 40 mg of virulent tubercle bacteria per os or 1 mg subcutaneously. It is true that most dogs have shown a greater increase of the skin thickness after BCG vaccination and/or virulent infections than before inoculation. But in most cases the difference has been so small that it lies at the limit of erroneous subjective measure.

The reactions have on the whole become greater, the greater the amount of allergizing substance given. This might be indicative that dog requires larger infection doses than have been given here, in order to develop at all a distinctly specific allergy so great that it is manifested with the tuberculin applied. It might, however, be thought that the allergy would be more easily detectable with other amounts of tuberculin.

5,000 I.U. OF TUBERCULIN

Normal dogs.

In 4 tests on 3 normal dogs reactions of 1—3 mm (15—60 per cent) have been recorded. With the erroneous subjective measures in mind the limit of non-specific reaction with 5,000 I.U. may be set at 3.5 mm or c. 80 per cent of increase.

In 5 tests on 4 other normal dogs (Table No. 4, a) the maximum reactions with 5,000 I.U. of tuberculin on the thorax were 0.5—2 mm (17—50 per cent).

BCG-vaccinated dogs.

In none of the dogs were reactions shown which distinctly exceeded the limit of non-specific reaction.

Dogs infected with virulent tubercle bacteria.

Of the perorally infected dogs (Nos. 3/50, 5/50, 7/50) none showed any distinctly positive reaction (2—3.5 mm or 46—140 per cent). In 1 of them (No. 7/50) 1 reaction might be called dubious (test on the 19. May 1951).

The dogs that were subcutaneously infected after preceding vaccination (Nos. 2/50, 4/50, 6/50) showed a rather distinct tendency to specific allergy with reactions of 3.5—4.5 mm (54—200 per cent).

Of the 2 non-vaccinated, subcutaneously infected dogs one gave a reaction of 3 mm (120 per cent) and the other 5.5 mm (73 per cent).

Assessed by the increase of the skin fold thickness, the tests then seemed to show a somewhat more sharply marked reaction in infected dogs when greater doses of tuberculin (5,000 I.U.) were used. In part of the tests which showed the greatest increase of the skin fold thickness there were also other signs of reaction, notably in the form of visible exudation and later crusting at the site of injection. This was observed in nearly half of the tests in infected dogs. But exudation as well as visible oedema was also observed in 2 out of 4 tests in normal dogs.

The total impression was that the large tuberculin dosis on the whole gave reactions with a better marked response than doses of 1,500 I.U. in presumably allergic dogs. But the non-specific reactions in normal dogs were also correspondingly more vehement with 5,000 I.U., which probably increases the possibility of erroneous positive reactions.

750—1,000 I.U. OF TUBERCULIN

Normal dogs.

In 2 normal experimental dogs the reactions were in 2 tests 0—1.5 mm (0—30 per cent).

In 8 tests on 4 other normal dogs (Table No. 4, a) reactions of 0—2 mm (0—50 per cent) were recorded. Error of measuring considered, the limit of non-specific reaction might be set at 2.5 mm (60 per cent).

BCG-vaccinated dogs.

In 1 dog (No. 5/50) the reaction may be called dubious, whilst the 4 other dogs showed non-specific reactions.

Dogs infected with virulent tubercle bacteria.

The non-vaccinated, subcutaneously infected dog (No. 1/50) gave a reaction which may be considered as faintly positive or dubious, whereas the other reactions had to be called undoubtedly non-specific when comparing them with reactions in normal dogs.

All in all, tests with small amounts of tuberculin have given fainter reactions in dogs in normal condition as well as after vaccination and/or virulent infection. The responses to the inoculations were on the whole so slight that they lay within the limits of measuring errors. One exception was dog No. 1/50, which showed a distinct tendency to positive allergy even with a small dose of tuberculin. Post mortem examination showed more clearly in this dog than in the other cases that the inoculation had taken.

Even if the number of observations with small amounts of tuberculin is relatively small, the result is indicative that c. 1,500 I.U. of tuberculin is probably quite as delicate an indicator as the small doses of tuberculin.

2. Hospital cases (Table No. 4).

In the years 1949—52 intracutaneous tests with Old Tuberculin have also been performed on dogs brought in for examination in the hospital, partly because they might be suspected of tuberculosis, partly without any such suspicion existing. In some of them a sickly condition could not be detected at all; 2 dogs suffered from tuberculosis, whilst most of the hospital cases were suffering from other, non-tuberculous diseases.

Normal dogs.

In 20 dogs, in which no disease or infection could be detected, 28 tests were performed with the usual amounts of tuberculin. For further control, 15 I.U. and 150 I.U. of tuberculin and 0.1 ml of 0.9 per cent NaCl were injected simultaneously in 1 dog. 3 dogs were later examined post mortem, and no signs of tuberculous infection were found.

In all dogs, except one, the maximum reactions did in no instance exceed 2 mm or 50 per cent, which was observed after smaller as well as after greater amounts of tuberculin. Thus the reactions were found within the same limits as in the normal experimental dogs.

1 dog, however, represented a clear exception, giving reactions of 4.0—4.5 mm or 57—80 per cent in different tests within 2 weeks'

interval. These reactions cannot be assessed as negative, notably compared to contemporary reactions in its litter mate, in which maximum reactions of 1—2 mm or 13—29 per cent were observed. These 2 dogs were kept together and tended in exactly the same way for years, the only difference being that the first mentioned dog had been fed 413 g of thiouracil in the course of 8 months prior to the tests. It is hard to tell if the administration of thiouracil might account for the false "positive" reaction. *Long et al.* (1951) have observed that propyl-thiouracil inhibits the desensibilization toward tuberculin which is induced by the ingestion of alloxan in BCG vaccinated guinea-pigs, and *Leech & Paterson* (1952) have found that thiouracil increases the reaction on PPD tuberculin in BCG vaccinated guinea-pigs. But the dog had not been BCG vaccinated, and post mortem no signs of tuberculous infection could be detected.

Table No. 4.

Maximum reactions with Old Tuberculin in Hospital cases.

Tuberculin		Max. increase in skin fold thickness		No. of dogs	No. of observations
I.U.	Type	mm	per cent		
		a. Normal dogs.			
5,000	D	0.5—2.0	25—50	3	4
5,000	F	0.5	17	1	1
1,500	V	0 —2.0	0—44	12	15
1,000	F	0 —0.5	0—13	1	2
750	V	0 —2.0	0—50	3	6
150	V	2.0	40	1	1
15	V	1.0	17	1	1
0	NaCl	0.5	7	1	1
		b. Dog, fed thiouracil.			
1,500	V	4.0—4.5	57—80	1	3
		c. Dogs suffering from different non-tuberculous diseases			
5,000	D	1.0—2.0	33—67	7	7
5,000	F	0.5—1.0	25—33	2	2
1,500	V	0 —2,5	0—57	11	12
1,000	F	0 —1.0	0—25	2	2
750	V	1.0—1.0	17—17	1	2

Dogs suffering from different, non-tuberculous diseases.

20 dogs were tested, of which 11 were later examined post mortem without showing any signs of tuberculous infection. The following diagnoses were represented: Tumores maligni (3 cases), lymphadenosis (1), arthrosis deformans (2), insufficientia renum chronica (2), insufficienta cordis chronica (2), gastritis catarrhalis chronica (2), cirrhosis hepatis (1), bronchopneumonia chronica (1), bronchitis subacuta (2) rhinitis chronica purulenta (1), epididymitis chronica (1), pyorrhoea (1), acanthosis nigricans (1).

In most of the 25 tests performed, the maximum reactions did not exceed the reactions found in normal dogs. In 1 test with 1,500 I.U. the absolute increase was slightly higher (2.5 mm). In 2 tests with 5,000 I.U. and in 1 test with 1,500 I.U. the relative increase slightly exceeded 50 per cent (60, 67 and 57 per cent respectively).

Dogs with spontaneous tuberculosis.

Only 2 cases were recorded. In 1 case, the reaction with 1,500 I.U. of the type V was 2.5 mm or 83 per cent. In the other case the reaction with 5,000 I.U. of the type D was 1.0 mm or 25 per cent. The first mentioned reaction might be deemed possibly dubious, while the last one must be assessed altogether negative. Both dogs were severely sick, nearly moribund, at the time of testing. This fact might possibly — at least partly — be the explanation for the apparent unreliability of the tuberculin tests.

3. Discussion.

In order to detect as many dogs as possible that have been exposed to tubercle bacteria, the limit of specific positive reaction should be set as low as possible, though without risking erroneous "positive" reactions. The chosen limits of specific reaction therefore were based upon the maximum non-specific reactions observed, to which a possible subjective error of measuring (0.5 mm or c. 20 per cent) was added. The percentage of positive reactions actually observed in infected or vaccinated dogs was small, thus indicating the unreliability of the intracutaneous test with Old Tuberculin (Table No. 5).

The reactions with 1,500 I.U. of tuberculin were submitted to statistical analysis, based upon the distribution of reactions shown in table No. 6. From this it appears that, with c. 95 per cent of probability — i. e., c. 5 per cent of erroneous positive reactions — the limit of specific reaction with 1,500 I.U. may be set at 2.2 mm (2.7 mm, when considering a subjective error of measuring). When also a probability of c. 5 per cent of erroneous negative reactions is considered, the limit of non-specific reaction would be 0.6 mm. This means that within the range of 0.6—2.2 mm, the reactions must be considered dubious. Within this range one will have to expect — from the present results — to find about 77 per cent of all reactions in non-infected dogs and about 63 per cent of all reactions in infected dogs, i. e., an extensive overlapping, greatly reducing the possibility of distinguishing between infected and non-infected dogs (cf. Graph I). Only a small percentage of distinctly positive reactors should be expected among infected and/or vaccinated dogs. Even with 5,000 I.U. of tuberculin, which has seemingly shown the best agreement of the status of infection and the allergic reaction to tuberculin, only about 50 per cent of reliability was found.

There is on the whole a marked tendency to greater skin reactions after infection or vaccination than in the same dogs in normal condition, indicating that the dogs have indeed developed a certain degree of tuberculin allergy as a consequence of the inoculations. But rather often the allergy has not been strong enough to produce a significant skin reaction with the tuberculin applied. Visible reactions (hyperaemia, oedema and exudation) were observed in some tests in infected dogs. But this was also observed in normal dogs after injection of 1,500—5,000 I.U. of tuberculin.

In Table No. 3 is also shown the juncture when the increase in skin fold thickness reached its peak. A simple estimation of the figures shows that in non-infected dogs the punctum maximum enters in the course of the first 24 hours after injection in c. 67 per cent of the tests and stays for 48—72 hours in c. 61 per cent. (When adding the figures observed in non-tuberculous, hospital cases, the mean figures would be c. 80 per cent and 48 per cent respectively). In vaccinated dogs, c. 80 per cent of the reactions reach the punctum maximum in the first 24 hours, and c. 53 per cent persist at this maximum for 48—72 hours. In infected dogs, the reaction reaches its maximum in the course of the first 24 hours in c. 40 per cent and stays at the point of maximum for 48—72 hours in c. 82 per cent. There is then a tendency to culmination in the course of the

first 24 hours in non-infected and vaccinated dogs, whereas the reaction in infected dogs in most cases chiefly reaches its point of maximum at a later juncture (after 48—72 hours).

Table No. 5.

Reactions with Old Tuberculin laterally on the thorax.

	750-1,000 I. U.			1,500 I. U.			5,000 I. U.		
	mm	per cent	n	mm	per cent	n	mm	per cent	n
Maximum non-specific reaction	2.0	50	14	2.5	57	39	3.0	67	18
Choice of limits of specific reaction	2.5	60		3.0	70		3.5	80	
Per cent positive reactions in experimentally infected dogs	8	38	13	15	35	20	50	55	20
Per cent positive reactions in BCG vaccinated dogs	20	0	5	40	40	5	40	0	5

n: Number of observations.

Table No. 6.

Distribution of maximum reactions with 750—5,000 I.U. of Old Tuberculin on the thorax.

Maximum increase, mm	750-1,000 I. U.				1,500 I. U.				5,000 I. U.			
	N	A	I	V	N	A	I	V	N	A	I	V
0	1	4				2						
0.5		1	2		1	8	2			3		
1		4	5	8	5	6	2		1	2		
1 5	1	2	2	1	3	6	6			4		1
2		1	3		3	4	3	1	1	5	2	
2.5						1	4	2	1		3	1
3			1	1			3	1	1		5	1
3.5								1			4	2
4											3	
4.5											2	
5												
5.5											1	

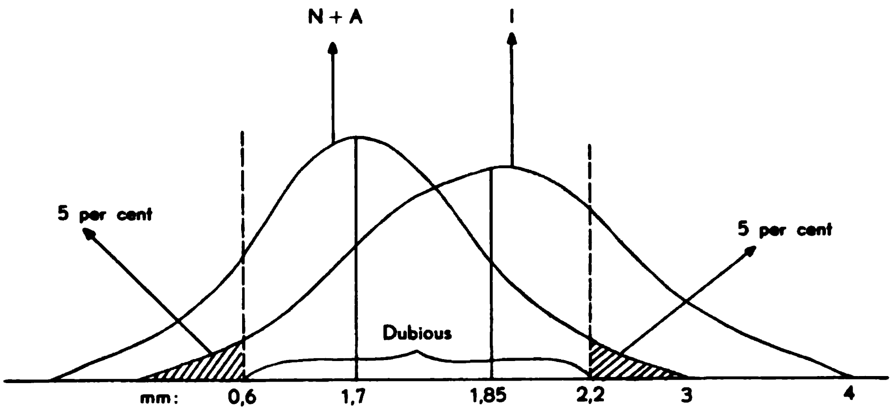
N, I and V: The same denominations as in Table No. 3.
A: Hospital cases (Table No. 4, a and c).

Graph 1.

Statistical analysis of reactions with 1,500 I.U. of Old Tuberculin.

N+A = Non-infected dogs (normal + other, non-tuberculous conditions).

I = Infected dogs.



II. HEAT CONCENTRATED SYNTHETIC MEDIUM (HCSM) TUBERCULIN

Because of the unsatisfactory results obtained with Old Tuberculin in dogs, it was advisable to investigate the efficiency of other types of tuberculin. As soon as a Norwegian product of Heat Concentrated Synthetic Medium (HCSM) Tuberculin was available (1953), tests with this type of tuberculin were started on experimental dogs as well as on hospital cases.

The tuberculin was produced from tbc. of the typus humanus (stock "E 9655" at The State Veterinary Institute, Oslo). According to *Svenkerud* (personal communication, 1954), the potency of this tuberculin corresponds to the International Standard Tuberculin, and it contains 6 mg of protein per ml. It was chiefly used in 3 dilutions (in 0.9 per cent NaCl), containing 3.0 and 0.3 and 0.03 mg of protein per ml. The volume injected was always 0.1 ml, i. e., each dosis containing 5,000 and 500 and 50 I.U. of tuberculin respectively. Simultaneously, 0.1 ml of the diluent (physiological saline solution) was injected for control. The injections were made intracutaneously,

laterally on the thorax behind the shoulder, mostly in the middle part (T).

After cutting off the hairs with scissors, the site of injection was depilated. At first, a concentrated aquaeous suspension of Barium sulphide was used for this purpose. It had, however, to be abandoned, as it some times produced a swelling of the skin in 24 hours. Later, a depilatory sulphide containing cream ("Veet") was used. Apart from the first application, (in 2 normal dogs), the depilatory cream was altogether satisfying. But for safety sake the depilation was regularly done 24 hours before the injection of tuberculin.

Readings were done with a cutimeter in the way already described for tests with Old Tuberculin. Besides, assessments after Aronson's method were undertaken (see later).

1. Experimental dogs.

3 litters of middle-sized mongrels, born and reared in isolation, were used. 9 dogs were inoculated with virulent tbc. of the typus humanus at the age of 13 to 21 months. 2 of them (Nos. 13/52 and 14/52) were infected from a c. 4 weeks old culture on liquid synthetic medium (strain "E 9655", from The State Veterinary Institute, Oslo). 3 dogs (Nos. 9/52, 10/52 and 22/52) were inoculated with a c. 2 weeks old culture of the same strain. 4 dogs (Nos. 11/52, 12/52, 16/52 and 17/52) were infected from a c. 8 weeks old culture on Petragnani's solid medium (strain No. "413", from The State Veterinary Institute, Oslo, originally isolated from a dog). All inoculations were made intraperitoneally. 1 dog was given c. 5 mg of tbc. (dog No. 13/52), the other dogs c. 10 mg. — 1 dog (No. 8/52) was not inoculated (normal control).

The clinical and post mortem findings may be summarized as follows (cf. Table No. 7):

6 dogs showed no clinical reaction at all. In 3 dogs a moderate general reaction occurred c. 4 weeks after inoculation: moderate fever and depression of vivacity, appetite and body weight, lasting for 1 to 2 weeks. Simultaneously, an exudative inflammation developed in the abdominal wall with fistulae to the skin surface at the site of injection. Tbc. could not be detected in the urine.

Autopsies and histological examinations were done at the Institute of Pathology, The Veterinary College of Norway (S. Erichsen). In 5 dogs, macroscopic, local tuberculous processes were found (in the abdominal wall in dogs Nos. 12/52, 16/52, 17/52, 22/52 and in the

Table No. 7.
Experimental Infection. Series No. 2.

Dog No.	Days of obs.	Weight differ. kg	Clin. sympt.	Post mortem				
				Aut	Hist	Smears	Culture	Inoculation in guinea pigs
9/52	70	+ 0.5	0	0	+?	+	0	0
10/52	70	÷ 0.4	0	+	+	+	0	+
22/52	70	÷ 0.1	0	+	+	+	0	+
13/52	60	+ 0.1	0	0	0	0	0	+
14/52	60	+ 02	0	0	0	+		+
11/52	50	+ 0.8	0	0	+	+	0	0
12/52	50	÷ 0.4	+	+	+	+	0	+
16/52	44	÷ 2.4	+	+	+	+	0	+
17/52	44	÷ 1.6	+	+	+	+	0	+
8/52 Control		÷ 4.5	0	0	0	0	0	0

Abbreviations as in Table No. 2

A recent pregnancy finished a couple of weeks before euthanasia explains the loss of body weight in the control dog.

intestinal wall in dog No. 10/52). In 1 dog (No. 16/52) submiliary foci were also observed in the liver. Histologically, besides the processes already mentioned, changes of possibly tuberculous structure were found in the liver of 1 dog (No. 11/52) and in the lgll. bronchiales in 1 dog (No. 9/52).

In 8 of the 9 infected dogs, acid fast rods were found in smears from one or several organs. In 7 cases, inoculation of suspected material from the dogs into guinea pigs produced tuberculous processes in those (from dog No. 13/52: spleen; dog No. 14/52: spleen and liver; dog No. 16/52: abdominal wall and kidney; dog No. 17 52: abdominal wall; dog No. 12/52: abdominal wall, spleen and lumbar lymph nodes; dog No. 10/52: intestinal wall, spleen, liver and mesenteric lymph nodes; dog No. 22/52: abdominal wall). In the non-infected dog (No. 8 52) no tuberculous lesions or tbc. could be detected.

From these experiments may be concluded that in dogs there is a high natural resistency even against intraperitoneal inoculation of rather large amounts of tbc. (cf. also *Lasserre et al.*, 1941).

Several authors (cf. *Cobbett*, 1907, *Lewis & Montgomery*, 1913, *Mills & Colwell*, 1937, *Mills, Barth & Gunn*, 1940, *Gunn & Mills*, 1940, *Lasserre et al.*, 1941, *Gunn, Sheehy, Colwell & Mills*, 1942, *Gunn, Mills, Shepard & Barth*, 1943, *Gunn & Sheehy*, 1950) have experienced that intrabronchial (intratracheal) inoculation of tbc. is more dangerous to dogs, as it regularly seems to produce a fatal pneu-

Table No. 8.

0.1 ml of HCSM Tuberculin on the thorax.

Experimental dogs. Series No. 2.

Dog No.	Days 1) after infection	Tuberculin I. U.	Skin fold measure: before inject.	Skin fold measure: max. increase mm	Skin fold measure: max. increase per cent	P. M.	Assessment ad modum Aronson 24	Assessment ad modum Aronson 48	Assessment ad modum Aronson 72
9/52	0	5,000	3.5	1	29	24	+	+	0
		500	3.5	1	29	24	+	0	0
		50	3.5	0.5	14	24-48	+	?	0
		0	4	0	0	0	0	0	0
	9	5,000	3	2.5	83	24-72	?	+	+
		500	3	1.5	50	24-72	++	+	+
		50	4	0	0	0	+	+	+
		0	4.5	0	0	0	0	0	0
	63	5,000	3	4	133	48-72	+	+	+
		500	3	2.5	83	48	+	+	+
		50	3.5	0.5	14	24-48	+	+	+
		0	3.5	0	0	0	0	0	0
10/52	0	5,000	5.5	2	40	24	+	0	0
		500	5.5	0.5	9	24	0	0	0
		50	6	0.5	8	24-48	0	0	0
		0	6.5	0.5	8	24	0	0	0
	9	5,000	4	2.5	63	24-72	++	++	++
		500	4.5	1.5	33	24-72	++	++	++
		50	5	0.5	10	24-48	++	++	++
		0	4.5	0.5	11	24	0	0	0
	63	5,000	4.5	4	89	24-72	++	++	++
		500	4.5	2.5	56	48	++	++	++
		50	5.5	0	0	0	+	+	+
		0	5.5	0	0	0	0	0	0
22/52	0	5,000	3.5	0.5	14	48-72	0	0	0
		500	4	0	0	0	0	0	0
		50	4	0	0	0	0	0	0
		0	4	0	0	0	0	0	0
	9	5.000	2.5	2	80	24-72	++	++	++
		500	2.5	1	40	24-72	++	++	++
		50	2	1	50	24-72	+	0	0
		0	2.5	0.5	20	24-72	0	0	0
	63	5,000	3.5	4.5	129	24	+	+	+
		500	3.5	2.5	71	72	+	+	+
		50	3.5	1.0	29	24-72	+	+	+
		0	4	0.5	13	24	0	0	0
13/52	9	500	6	4	67	24-72	+	++	++
		50	6	2	33	48-72	0	0	0
		0	6	0.5	8	48-72	0	0	0
	45	5,000	6	4	67	72	+	+	+
		500	6	2.5	42	72	+	+	+
		50	6.5	2	31	48	0	0	0
		0	7	1	14	48	0	0	0
14/52	9	500	5.5	2.5	45	48	+	++	+
		50	5.5	1	18	48	0	+	0
		0	5.5	0.5	9	48	0	0	0
	45	5,000	5	5	100	48	+	+	+
		500	6	3	50	48	+	+	+
		50	6	2.5	42	48	0	0	0
		0	6.5	0.5	8	24-72	0	0	0

1) o days = before infection.

Table No. 8 (continued).

Dog No.	Days after infection	Tuberculin I. U.	Skin fold measure before inject	max. increase mm	max. increase per cent	P. M.	Assessment ad modum Aronson 24	48	72
11/52	0	5,000	4.5	1.5	33	24	0	0	0
		500	4.5	1	22	24	0	0	0
		50	5	0.5	10	24	0	0	0
		0	5	0	0	0	0	0	0
	40	5,000	4.5	3	67	48	++	++	+
		500	4	3	75	24-48	++	++	+
		50	4	1·5	38	48-72	+	+	+
		0	4	0.5	13	48-72	0	0	0
12/52	0	5,000	3.5	1	29	24	0	0	0
		500	4	0.5	13	24	0	0	0
		50	4	0	0	0	0	0	0
		0	4	0	0	0	0	0	0
	40	5,000	3.5	4	114	48	++	++	++
		500	3	3.5	117	48	++	++	+
		50	3	1.5	50	24-48	+	+	+
		0	3	0	0	0	0	0	0
16/52	0	5,000	7	0	0	0	0	0	0
		500	7	0	0	0	0	0	0
		50	7	0	0	0	0	0	0
		0	7	0	0	0	0	0	0
	40[2])	5,000	11	7	64	48	+++	+++	++
		500	9	5	56	72	++	++	+
		50	8	2	25	24-48	++	++	+
		0	7	0	0	0	0	0	0
17/52	0	5,000	7.5	0	0	0	0	0	0
		500	8	0	0	0	0	0	0
		50	7.5	0	0	0	0	0	0
		0	7.5	0	0	0	0	0	0
	40[2])	5,000	11	6.5	59	48	+++	++	++
		500	9	5	56	48-72	++	++	++
		50	8	2	38	48	++	++	++
		0	8	0	0	0	0	0	0
8/52	Normal, control	5,000	3	1.5	50	24	0	0	0
		500	3.5	0.5	14	24-72	0	0	0
		50	4	0.5	13	24	0	0	0
		0	4	0	0	0	0	0	0
	Normal, 12 weeks later	5,000	3	2	67	24	+	+	0
		500	3	1	33	24-72	+	+	0
		50	4	0	0	0	0	0	0
		0	4	0	0	0	0	0	0
	Normal, 19 weeks later	5,000	3	2.5	83	24	+	0	0
		500	3	0.5	17	24-72	0	0	0
		50	3	0.5	17	48-72	0	0	0
		0	3.5	0	0	0	0	0	0

2) Injections made high dorsally on the thorax.
In the dogs No. 13/52 and 14/52 the tests before infection were unsuccessful because of skin irritation caused by depilation.

monia in 2 or 3 months (typus humanus and bovinus). But this mode of infection was not chosen in the present experiments, because the chief purpose was an investigation of the tuberculin reaction, and under these circumstances infections which most probably might produce fatal tuberculosis in a short time were not desirable.

Results (Table No. 8).

Maximum reactions were observed as follows:

5,000 I.U. OF TUBERCULIN

Before infection: 0—2.5 mm or 0—83 per cent (10 tests in 8 dogs). 2 tests in 2 dogs had to be left out of consideration because of nonspecific irritation of the skin due to depilation.

9 days after infection: 2—2.5 mm or 63—83 per cent (3 tests in 3 dogs).

40-63 days after infection: 3—7 mm or 59—133 per cent (9 tests in 9 dogs).

500 I.U. OF TUBERCULIN

Before infection: 0—1 mm or 0—33 per cent (10 tests in 8 dogs).

9 days after infection: 1—4 mm or 33—67 per cent (5 tests in 5 dogs).

40—63 days after infection: 2.5—5 mm or 42—117 per cent (9 tests in 9 dogs).

50 I.U. OF TUBERCULIN

Before infection: 0—0.5 mm or 0—17 per cent (10 tests in 8 dogs).

9 days after infection: 0—2 mm or 0—50 per cent (5 tests in in 5 dogs).

40—63 days after infection: 0—3 mm or 0—50 per cent (9 tests in 9 dogs).

0.9 PER CENT NaCl:

Before infection: 0—0.5 mm or 0—8 per cent (10 tests in 8 dogs).

9 days after infection: 0—0.5 mm or 0—20 per cent (5 tests in 5 dogs).

40—63 days after infection: 0—1 mm or 0—14 per cent (9 tests in 9 dogs).

When assessed by the absolute reaction (mm), all dogs have shown greater reactions 40—63 days after infection than was ob-

served in any of them before infection, when 5,000 and 500 I.U. of tuberculin were injected. With 50 I.U. of tuberculin, the reactions increased in most of the dogs, but they were far less significant than with the greater doses of tuberculin. In 2 dogs the reaction did not increase at all with 50 I.U. The non-specific reaction with 0.9 per cent of saline solution kept within the same minimum limits before and after infection.

When judged by the relative increase in skin fold thickness (per cent), the differences before infection and 40—63 days after infection were slightly less with 500 I.U. and considerably less with 5,000 and 50 I.U. of tuberculin, as compared to the same reactions assessed by the absolute increase.

2. Hospital cases (Table No. 9).

91 dogs were tested with HCSM Tuberculin.

Normal dogs.

25 dogs, which appeared clinically normal and in which tbc. could not be detected in tracheal mucus or urine, were tested. One of them was later autopsied, where no signs of tuberculous infection were observed. From table No. 9 may be seen that the reactions do not deviate clearly from the reactions found in the normal experimental dogs.

Dogs suffering from different, non-tuberculous diseases.

62 dogs were tested, of which 29 were later examined post mortem, where no signs of tuberculous infection were found.

The diseases represented were: Tumores maligni (10 cases), tumor benignus (1), lymphadenosis (2), splenomegalia (1), anaemia aplastica gravis (2), aneurysma dissecans aortae (1), myositis chronica eosinophilica et atrophicans (1), encephalopathia chronica (1), diabetes mellitus (1), gonitis chronica aseptica (1), fissura metacarpi (1), intoxicatio exogena incognita (1), hypertrophia prostatae (1), insufficientia renum chronica (11), insufficientia cordis chronica (5), myocarditis (1), helminthiasis intestinalis (1), gastro-enteritis catarrhalis chronica (3), cystitis catarrhalis chronica (1), cirrhosis hepatis (1), hepatitis chronica purulenta (1), ascites (1), haemocoelia (1), emphysema pulmonum chronicum (2), pleuritis chronica adhaesiva (2), bronchopneumonia chronica (3), bronchitis chronica (9), rhinitis chronica purulenta (1), laryngitis catarrhalis (1), tracheitis catarrhalis chronica (3), conjunctivitis chronica (1),

metritis chronica purulenta (3), balanitis chronica purulenta (1), bursitis para-analis purulenta (1), abscessus subcutaneus (1), dermatosis chronica (1), atheromatosis (1), furunculosis chronica (3), otitis externa chronica (1), scabies aurium (1), febris catarrhalis (1), sepsis (2), cachexia (1).

From the figures in Table No. 9 appears that the reactions in dogs suffering from different, non-tuberculous diseases do not exceed the limits of reactions in normal dogs.

Table No. 9.

Maximum reactions with HCSM Tuberculin in Hospital cases.

Tuberculin I. U.	Max. increase in skin fold thickness mm	Max. increase in skin fold thickness per cent	No. of dogs	No. of observations
	a. Normal dogs.			
5,000	0 -2.5	0·125	24	25
2,500	0.5 -2.5	33-125	8	9
2,000	0 -1.5	0- 56	12	12
1,700	0 5 -1.0	8- 33	5	5
1,000	0.75	27	1	1
500	0.5 -2.0	5- 89	10	10
100	1.25	38	1	1
50	0 -1.0	0- 40	7	7
0 (NaCl)	0 -1.0	0- 33	25	26
	b Dogs suffering from different non-tuberculous diseases.			
5,000	0 -2 75	0·157	55	60
2,500	0 -2.75	0-157	36	36
2,000	0 -2 0	0- 40	11	13
1,700	0 -1.0	0- 57	5	5
1,000	0 -1.5	0- 71	10	10
500	0 -1 5	0- 50	21	23
100	0 -0 5	0- 17	2	2
50	0 -1.5	0- 25	16	18
0 (NaCl)	0 -1.0	0- 33	55	58

Dogs with advanced spontaneous tuberculosis (Table No. 10).

Only in 4 cases has the opportunity been established to perform tests with HCSM Tuberculin. The diagnosis was verified post mortem.

In 1 dog, which was moribund at the time of testing, the reactions with 500 and 50 I. U. of tuberculin were altogether negative (dog No. 195—52/53). In another dog (No. 159—52/53), the reaction with

2,500 I. U. was dubious, compared to maximum reactions in normal dogs. There was no opportunity of re-testing this dog before euthanasia. In the 2 remaining dogs (No. 164—52/53 and 110—53/54), however, the reactions with 500 to 5,000 I. U. were significantly positive, markedly exceeding the maximum reactions in normal dogs.

Table No. 10.

0.1 ml of HCSM Tuberculin on the thorax.
Hospital cases with advanced spontaneous tuberculosis.

Dog No.	Tuberculin I. U.	Skin fold measure			P. M.	Notes
		before inject	max. increase			
			mm	per cent		
159—52/53	2,500	2	2	100	24	Abdominal tub.
164—52/53	2,500	3.5	3.5	100	72	Abdominal tub.
195—52/53	500	5	1.5	30	24—48	Generalized tub.
	50	5	0.5	10	24—48	
	0	5	0.5	10	24	
110—53/54	5,000	2.5	10.5	420	72	Pulmonary tub.
	500	2.5	4.5	180	72	
	50	2.5	1	40	48—72	
	0	2.5	0.5	20	24—48	

3. Discussion.

Non-specific reaction in non-tuberculous dogs.

The maximum non-specific reactions in normal experimental dogs were found to be 2.5 mm or 83 per cent with 5,000 I.U., 1.5 mm or 40 per cent with 500 I.U. and 1.0 mm or 40 per cent with 50 I.U. of HCSM Tuberculin. In 30 tests with physiological saline solution a non-specific increase in skin fold thickness of up to 0.5 mm or 25 per cent was observed. Taking a possible subjective error of measuring into consideration, the limits of specific reaction to be chosen would be as appears from table No. 11.

In hospital cases with more or less unknown history as to the possibility of the dogs having been exposed to tuberculous infection, but without showing any signs of such infection — bacterioiogical examination of the tracheal mucus and urine included —, most of the reactions were found within the same limits as for the experimental dogs before infection. In 1 observation out of 33 with 500

I.U. of tuberculin, the reaction touched the limit (2 mm) (Dog No. 470-53/54). By relative assessment the reaction in this dog slightly exceeded the limit set, and in 2 other dogs the reaction touched this limit (50 per cent) (Dogs Nos. 286-53/54 and 152-54/55).

With 5,000 I.U. no reactions reached the limit set for specific reaction by absolute reading (85 tests). By relative assessment, 4 reactions touched the proposed limit (100 per cent) (Dogs No. 470-53/54, No. 120-54/55, No. 324-55/56 and No. 351-55/56), and 2 reactions exceeded the limit (Dogs Nos. 286-53/54 and 152-54/55).

With 50 I.U., 2 out of 25 reactions touched the limit set (1.5 mm) (Dogs No. 190-53/54 and No. T 1/54). The relative increase, however, was in both cases only 23 per cent.

Thus the limits of specific reaction chosen from the results in experimental dogs, seem justified, and they would most likely mean very little risk of obtaining false positive reactions.

In the hospital cases even doses of 100, 1,000, 1,700, 2,000 and 2,500 I.U. of HCSM Tuberculin were used. With 100 I.U. the reactions were found within the same range as for 50 I.U. (3 tests only). With 1,000-2,000 I.U. the reactions did not exceed those with 500 I.U., except for 1 test with 2,000 I.U. (2 mm in dog No. 230-54/55), thus indicating that the limit should be set as for 500 I.U. (2 mm or 50 per cent). With 2,500 I.U. the maximum reactions were 0—2.75 mm or 0—157 per cent, thus lying within the same range as for 5,000 I.U. as assessed by the absolute increase, and in 4 tests (out of 45) even exceeding them when estimated by the relative increase. This would indicate that the limit of specific reaction with 2,500 I.U. should not be set lower than for 5,000 I.U.

The assessment by the relative increase in skin fold thickness might be expected to be less reliable than assessment by the absolute increase (cf. p. 13). The experiences with HCSM Tuberculin seem to substantiate this opinion.

Specific reactions in dogs infected with tbc.

40 to 63 days after infection, all reactions (100 per cent) exceeded the chosen limits of specific reaction with 500 and 5,000 I.U. of tuberculin, when assessed by the absolute increase, and 67 per cent exceeded the limit with 50 I.U. (Table No. 11). These results indicate that the intracutaneous test is most reliable, even in dogs, when the said mode of assessment and doses of 500—5,000 I.U. of HCSM Tuberculin are used. The contrast to the results with Old Tuberculin is striking.

In most cases even 50 I.U. of HCSM Tuberculin produced a greater skin reaction after than before the infection in the same dog. But the reactions were far less significant. In 2 dogs no specific response was observed. With such small doses of tuberculin the possibility of detecting specific tuberculin allergy is therefore considerably reduced.

Assessment by the relative increase was also far less reliable in infected dogs. In most cases the reactions might just be deemed dubious. Only 1 of the reactions in infected dogs (with 500 I.U. in dog No. 12/52) markedly exceeded the maximum reaction observed in non-tuberculous dogs.

As early as 9 days after infection an increasing skin reaction was observed (Table No. 8; 5 tests). The reactions were certainly less significant than 40—63 days after infection. But with 500 I.U. 4 reactions exceeded the maximum reactions in normal dogs, and the 5th touched this limit. With 5,000 I.U., 2 out of 3 reactions touched the limit of non-specific reaction. With HCSM Tuberculin in suitable doses there should therefore be a fair chance of detecting tuberculous infection at a very early point of time after a suspected exposure. This observation corresponds well to those of *Colwell & Mills* (1940*a*), who have found specific skin allergy to O.T. and P.P.D. in dogs 7-12 days after intra-tracheal infection.

The risk of getting erroneous negative (as well as erroneous positive) reactions should be very little with doses of 500—5,000 I.U. of HCSM Tuberculin, when assessed by the absolute increase in skin fold thickness. A statistical analysis of the reactions observed in experimental dogs fully supports this conclusion, presuming the limits of specific reaction be set at 3 mm for 5,000 I.U. and 2 mm for 500 I.U. (cf. Table No. 12). Supposing 95 per cent of probability, it shows a decided significance of difference between the reactions in normal and infected dogs with 500 I.U. of tuberculin, (calculated by the distribution-free methods).

Reactions in spontaneously tuberculous dogs.

The tests in spontaneously tuberculous dogs are quite inconclusive because of the small number of cases. However, the results at least do not contradict the results in experimentally infected dogs. It is true that in 1 of the 4 dogs the reaction with 500 I.U. of tuberculin was within the limits of non-specific reaction, and therefore had to be deemed negative. But this dog was in a moribund state at the time of testing.

Table No. 11.

Reactions with HCSM Tuberculin laterally on the thorax in experimental dogs.

	50 I. U.			500 I. U.			5,000 I. U.		
	mm	per cent	n	mm	per cent	n	mm	per cent	n
Maximum non-specific reaction	1	40	30	1.5	40	31	2.5	83	28
Choice of limits of specific reaction	1.5	50		2	50		3	100	
Per cent positive reactions 40—63 days after infection .	67	11	9	100	89	9	100	44	9

n: Number of observations.

Table No. 12.

Distribution of maximum reactions with 50—5,000 I.U. of HCSM Tuberculin on the thorax.

Maximum increase mm	50 I. U.			100 I. U.	500 I. U.			1,000—2,000 I. U.	2,500 I. U.	5,000 I. U.		
	N	A	I	A	N	A	I	A	A	N	A	I
0	5	11	1	1	3	4		6	6	2	11	
0.5	5	8a)	1	1	4	13		20	12	1	22	
1		3	1	1b)	3	9		15	10	2	23	
1,5		3	2			6		4	8	2	16	
2			2			1		1	5	2	6	
2.5			1				4		4c)	1	7d)	
3			1				2					1
3.5							1					
4												4
4.5												1
5							2					1
5.5												
6												
6.5												1
7												1

Denominations as in Table No. 6.
A: All dogs in Table No. 9.
I: Not including tests 9 days after infection.
a) 1 reading: 0,75 mm.
b) Exact reading: 1,25 mm.
c) 2 readings: 2,75 mm.
d) 1 reading: 2,75 mm.

4. Assessment ad modum Aronson.

The method that *Aronson* (1934) has used for estimation of the reaction in Mantoux's test in the forearm of man consist of measuring the diameter of visible changes at the site of injection, undertaken 24, 48 and 72 hours after injection. The assessment is made after the following form:

0	= negative: slight hyperaemia without oedema			
?	= dubious: slight hyperaemia with oedema less than 5 mm			
+	= faintly positive:	oedema	5—10 mm	
++	= markedly	"	"	10—20 mm
+++	= strongly	"	"	20—30 mm
++++	= very strongly positive: central necrosis			

Mills & Colwell (1937) and *Colwell & Mills* (1940, a and b) have found this method of reading applicable to dog. With 100 I.U. of O.T. or P.P.D. they found by measuring 48 hours after injection c. 90 per cent of reliability in experimentally infected dogs. They considered visible oedema of 5 mm of diameter a suitable limit of positive reaction in dog as in man.

In the tests with HCSM Tuberculin in experimental dogs (series No. 2) readings by Aronson's method were performed simultaneously (Tables No. 8 and 13).

Normal dogs.

In 5 dogs all reactions were negative (Nos. 11/52, 12/52, 16/52, 17/52 and 22/52). In 1 dog (No. 9/52) there was a faintly positive reaction with 5,000 I.U. after 24 and 48 hours, and with 500 and 50 I.U. after 24 hours. In another dog (No. 10/52) was found a faintly positive reaction with 5,000 I.U. after 24 hours. In the 8th dog (No. 8/52) which was tested thrice, all reactions were negative in the 1st test. In the 2nd test this dog reacted positively with 5,000 I.U. and 500 I.U. after 24 and 48 hours, and in the 3rd test slightly positively with 5,000 I.U. after 24 hours. With 50 I.U. the reaction was dubious in 1 dog (No. 9/52).

Infected dogs.

In infected dogs (9 days as well as 40—63 days after infection) all reactions with 5,000 and 500 I.U. were positive. With 50 I.U. 3 out of 14 tests were negative. 0.9 per cent of saline solution gave no positive reactions.

In infected dogs the reactions seemed to be as significant by Aronson's method as by measuring of the absolute increase of the skin fold thickness. But the relatively great number of erroneous positive reactions in non infected dogs lowers the usefulness of the method considerably. The results might be indicative that the limit of positive reaction must be set somewhat higher for HCSM Tuberculin in greater doses (500—5,000 I.U.).

Judging by these few observations, reading by Aronson's method in dog seems to be less exact and considerably more difficult than measuring of the folded skin. Yet the method of Aronson must be deemed a valuable supplementary mode of reading.

Table No. 13.

Per cent positive reactions with 0—5,000 I.U. of HCSM Tuberculin in experimental dogs, estimated ad modum Aronson.

No. of days after infection	NaCl		50 I. U.		500 I. U.		5,000 I. U.	
	per cent	n	per cent	n	per cent	n	per cent	n
0	0	10	10	10	20	10	40	10
9	0	5	80	5	100	5	100	3
40—63	0	9	78	9	100	9	100	9

Point of time of maximum reaction.

From table No. 8 may be seen that in non-infected dogs the reactions on the whole reached the point of maximum in the first 24 hours (95 per cent of the reactions), and only 20 per cent stayed at maximum beyond 24 hours. In infected dogs (40—63 days after infection) the point of maximum was reached at the earliest 48—72 hours in c. 83 per cent, and in c. 95 per cent of the reactions they stayed at the maximum 48—72 hours after injection. 9 days after infection there showed an intermediary reaction between the 2 groups mentioned: The Punctum maximum enters in most cases during the first 24 hours, but stays for 48—72 hours in all of them.

HCSM Tuberculin has shown a somewhat clearer difference between infected and non-infected dogs than has O.T. even when considering the juncture of culmination in skin reaction.

III. RELATION OF SKIN REACTION TO BLOOD REACTION

A study of the differential white blood cell picture in tuberculous and non-tuberculous dogs before and after tuberculinization has already been published *(Berg,* 1957), the result of which was that a certain degree of eosinopenic reaction occurs rather regularly 6 hours after injection of tuberculin in infected dogs.

In table No. 14 is set up a comparison of the maximum skin reactions and the number of eosinophile leucocytes 6 hours after the injection of HCSM Tuberculin in the same dogs before and after intraperitoneal infection with tbc. (7 dogs in experimental series No. 2).

Table No. 14.

Relation between skin reaction and eosinopenic blood reaction after injection of 500 and 5,000 I.U. of HCSM Tuberculin in 7 experimental dogs (from series No. 2).

Dog No.		Maximum increase in skin fold thickness				Percentage of eosinophiles			
		500 I. U.		5,000 I. U.		before inject. per cent	6 hours after injection		
		mm	per cent	mm	per cent		per cent	decrease absolute	decrease relative
9/52	N	1	29	1	29	7.5	4.0	3.5	40
	I 63	2.5	83	4	133	7.0	4.0	3.0	57
10/52	N	0.5	9	2	40	6.0	8.0	0 (+2)	0(+33)
	I 63	2.5	56	4	89	9.0	6.0	3.0	33
22/52	N	0	0	0.5	14	6.0	4.5	1.5	25
	I 63	2.5	71	4.5	129	9.0	2.5	6.5	72
11/52	N	1	22	1.5	33	5.5	10.5	0 (+5)	0(+91)
	I 40	3	75	3	67	4.5	4.5	0	0
12/52	N	0.5	13	1	29	5.5	4.0	1.5	27
	I 40	3.5	117	4	114	2.0	1.0	1.0	50
16/52	N	0	0	0	0	10.5	8.0	2.5	14
	I 40	5	56	7	64	3.0	2.5	0.5	17
17/52	N	0	0	0	0	7.5	5.5	2 0	27
	I 40	5	56	6.5	59	1.0	0	1.0	100

N: Normal (before infection).
I: After infection, 63 and 40 days respectively.

The skin reaction has in all cases increased significantly 40—63 days after infection. At the same time a tendency to a fall in number of eosinophile cells after tuberculin injection was observed, as compared to the blood reaction to tuberculinization before infection. But only in 1 of the 7 dogs (No. 22/52) the decrease of the number of eosinophiles is marked, tending towards the lowest limit observed in normal dogs. Thus there seems to be no warranted correlation between the degree of skin reaction and the degree of eosinopenic blood reaction. The comparison is also indicative that the skin reaction is a far more reliable sign of tuberculous allergy than is the blood reaction, as judged by differential counts of eosinophile leucocytes.

IV. SUMMARY AND CONCLUSIONS

Tests with Old Tuberculin.

In 8 experimental dogs 19 tuberculin tests before inoculation (normal condition), 15 tests 3—5½ months after BCG vaccination, and 59 tests 1—8 months after peroral and/or subcutaneous infection with human tubercle bacteria were undertaken. 60 tests in 49 hospital cases, of which 2 were suffering from spontaneous tuberculosis, were also carried out.

3 kinds of Old Tuberculin (2 of Norwegian and 1 of Danish manufacture) were applied, the single dose varying from 750 to 5,000 I.U. of tuberculin in 0,1 ml of volume. All tests were performed intracutaneously ad modum Mantoux. The skin was not prepared before injection, apart from cutting the hairs close with scissors. Reading was undertaken by measuring the thickness of the folded skin at the site of injection immediately before injection and 24, 48 and 72 hours later by means of an ordinary sliding gauge (cutimeter). The result was assessed by the maximum increase of the skin fold thickness, stated in mm (absolute increase) and in percentage of the pre-injection measure (relative increase).

The subjective error of measuring was satisfactory low, not exceeding 0.5 mm or 20 per cent.

Normally, the thickness of the skin fold varied individually in the same region of the body. Laterally on the thorax behind the shoulder, where all tuberculin injections were made, the skin fold averaged c. 5 mm (6 mm high dorsally, 4.5 mm in the middle and 3.1 mm ventrally).

Assessment by the absolute increase in skin fold thickness seemed preferable to judging by the relative increase.

In the experimental dogs in normal condition and in 30 tests in 20 other dogs in which no disease could be detected, the injection of Old Tuberculin regularly produced a certain non-specific reaction, the degree of which varied according to the dosis of tuberculin applied.

When taking the subjective error of measuring into consideration, the following limits of specific positive reaction were chosen: 2.5 mm (or 60 per cent) for 750—1,000 I.U., 3 mm (or 70 per cent) for 1,500 I.U. and 3.5 mm (or 80 per cent) for 5,000 I.U. of tuberculin. With these limits for assessment, the percentage of specific reactions in infected dogs was as follows: 50 per cent for 5,000 I.U., 15 per cent for 1,500 I.U. and 8 per cent for 750—1,000 I.U. of tuberculin, as estimated by the absolute increase of the skin fold thickness.

A statistical analysis of the reactions with 1,500 I.U. of tuberculin verified that the limits proposed for specific positive reaction were justfied, practically precluding false positive reactions. The statistical estimation also substantiated the conception that tests with Old Tuberculin must be of uncertain diagnostic value: With an admitted probability of 5 per cent of misses on either side (5 per cent of false positive and 5 per cent of false negative reactions) it cannot be expected that more than at most about 15 per cent of infected dogs should show so marked a skin reaction that it might be distinguished from non-specific reactions in non-infected dogs.

The large doses of tuberculin (5,000 I.U.) on the whole gave a greater percentage of positive reactions in infected dogs than did lower doses of tuberculin, though the non-specific reactions also seemed to increase with increasing amounts of tuberculin. But even with 5,000 I.U. the percentage of failures was c. 50 per cent.

In 2 tests with 1,500 and 5,000 I.U. of tuberculin on 2 dogs with advanced spontaneous tuberculosis, the reactions could not be assessed positive. It is, though, possible that the dogs were in an anergic phase, owing to the poor general condition.

In 25 tests on 20 dogs with other, non-tuberculous diseases, the reactions were under corresponding conditions not greater than in normal dogs. The risk of getting erroneous positive reactions should therefore be minimal, when using the proposed limits of specific reaction.

Yet the reaction in a normal dog, which for a long time had been fed thiouracil, should be set off as an exception, as the reaction had to be assessed positive in 3 different tests with 1,500 I.U. of tuberculin (4 and 4.5 mm).

The reactions mostly culminated at a later point of time in infected than in non infected dogs.

From the investigations, the general conclusion must be drawn that intracutaneous tests with Old Tuberculin in dogs are rather unreliable.

Tests with HCSM Tuberculin.

In 10 experimental dogs 70 tests were performed, namely 30 tests in 8 dogs in normal condition, 13 tests in 5 dogs 9 days after infection and 27 tests in 9 dogs 40 to 63 day after infection. Besides this 224 tests in 91 hospital cases were performed, of which 7 tests were on 4 dogs suffering from spontaneous tuberculosis.

The experimental infections were undertaken intraperitoneally with human tubercle bacteria. All tuberculin injections were made intracutaneously on the breast wall behind the shoulder. Before injection, the hairs were cut short with scissors, followed by depilation with commercial sulphide containing cream. Readings were done by measuring of the skin fold thickness (as for tests with Old Tuberculin). In the experimental dogs, readings of the diameter of visible changes at the site of injection (ad modum Aronson) were made simultaneously. The doses of tuberculin varied from 50 to 5,000 I.U. In all dogs, control injections of 0.9 per cent NaCl were given.

Considering a maximum subjective error of measuring, the following limits of specific reaction were chosen: 1.5 mm (or 50 per cent) for 50 I.U., 2 mm (or 50 per cent) for 500 I.U. and 3 mm (or 100 per cent) for 5,000 I.U. of tuberculin. Using these limits, all reactions with 500 and 5,000 I.U. in the dogs 40 to 63 days after infection, were clearly positive, when assessed by the absolute increase in skin fold thickness. With 50 I.U., only 67 per cent of the reactions in infected dogs were positive by this method of estimation. Assessment by the relative increase in skin fold thickness gave a considerably less degree of significance of specific reaction, even when the larger doses of tuberculin were used. A statistical analysis of the reactions with 500 and 5,000 I.U. substantiated the justification of the limits proposed, which should mean a minimal risk of false positive reactions.

Tests performed 9 days after infection indicate that tuberculous allergy may be detectable with HCSM Tuberculin at a very early point of time after exposure.

In hospital cases without detectable disease and in dogs with other, non-tuberculous diseases all reactions were lower than the limits set for specific reaction.

In 3 of 4 dogs with spontaneous tuberculosis 1 reaction was dubious and 2 were clearly positive. In the 4th dog the reaction with 500 I.U. was negative. But this dog was in a moribund state at the time of testing.

Assessment by measuring of the diameter of visible changes of the skin (ad modum Aronson) gave a relatively high percentage of positive erroneous reactions in non-infected dogs, thus being less reliable as compared to the measuring of the skin fold. But it might — under suitable conditions — prove to be a valuable supplement to this method of assessment.

The non-specific reactions in non-infected dogs as a rule culminated after 24 hours, whereas the specific reactions in infected dogs seldom reached maximum until 48 hours after injection.

Unlike Old Tuberculin, HCSM Tuberculin on the whole must be considered to have given very reliable and significant reactions in experimentally infected dogs, by means of which infected dogs could be distinguished from non-infected dogs, when doses of 500—5,000 I.U. of HCSM Tuberculin were injected. However, even this tuberculin may not always give significant positive reactions in dogs which are tested when being in a state of emaciation from progressive tuberculosis.

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The sooner the Cure of a Consumption is begun, the better it usually succeeds; and from hence this Distemper especially proves fatal, because the Physician is consulted when 'tis too late . . .

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From Södermanland County Sanatorium and the Central Tuberculosis Dispensary,
Löt, Malmby, Sweden.

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LONG-TERM PROGNOSIS IN PULMONARY TUBERCULOSIS DETECTED BY MASS RADIOGRAPHY

A County-Wide Survey with Controls and a Comparison Between Two Mass Surveys with a Seven-Year Interval

BY

IVAR KÄLLQVIST

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Shortly after I took up my present post at Södermanland County Sanatorium in 1952, the second mass radiographic survey of the County's general population was planned. My duties in this investigation gave me good insight into the many problems involved by mass radiography. Of great assistance were the records from the first survey of Södermanland. For the work underlying these records I am deeply indebted to the late Dr Willi Mascher, who conducted the survey.

That my studies of mass radiography and related questions developed along the lines shown here was largely due to the invaluable interest and encouragement of Docent Torsten Bruce of Söderby Sjukhus, to whom I express my heartfelt thanks. For stimulating discussions I am also grateful to Docent Stig Björkman of the Thoracic Clinic, Karolinska Sjukhuset.

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Strängnäs, December 1958.

Ivar Källqvist

INTRODUCTION

Many writers have described the primary results of mass radiographic surveys. Studies of the prognosis of mass-survey detected tuberculosis are fewer, and most are also in many respects incomplete. An important reason for this is the difficulty of following up the tuberculous persons, many of whom move from the surveyed area and take up residence elsewhere.

The present study comprises cases of pulmonary tuberculosis discovered by the first county-wide mass radiographic survey to be jointly organized by national and local authorities in Sweden. The survey took place in the County of Södermanland during the period October, 1946 to January, 1949. By investigating the fate of these cases I hoped to shed some light on the long-term value of county-wide mass radiographic surveys. A series of control cases of pulmonary tuberculosis is presented for comparison. These were discovered by the routine activities of the tuberculosis dispensary independently of the mass survey, but during the same period.

Since the tuberculosis situation has undergone a considerable change in the past decade, some findings from a second mass survey in Södermanland, from 1953 to 1955, are compared with corresponding results from the first survey. Although the follow-up period after this second survey is necessarily shorter than that after the first, the information which is already available reflects the change also in regard to long-term outlook for pulmonary tuberculosis.

CHAPTER I

EARLIER INVESTIGATIONS

1. *Mass radiography as a diagnostic aid*

For detection of pulmonary tuberculosis in its early, presymptomatic stages, roentgenographic examination is of decisive importance. Attempts to make such examination as simple and as cheap as possible, and thus suitable for mass population surveys, achieved success when the method of photographing a fluorescent X-ray screen with a small-film camera became available for practical use. In 1936 the first large-scale application of photofluorography was made in Brazil by *de Abreu* (1938).

Only six months after *Röntgen* in 1895 discovered the X-ray, *Bleyer* (1897) evolved an apparatus called a photofluoroscope, with which he photographed the fluorescent image. *MacIntyre* (1896), by placing a lead frame around the lens of the camera, prevented fogging of the photographic plates caused by direct radiation.

Porcher (1897), following experimental work, expressed the opinion that photofluorography was impractical and emphasized the advantages of direct roentgenography. *Köhler* (1907), on the other hand, described the practical potentialities of fluorography and, together with *Biesalski* (1909), devised a camera with an f/2.0 lens and a mirror arrangement by means of which the camera could be placed outside the beam of direct radiation.

In 1911 *Caldwell* prophesied, from experimental studies, the great future value of photofluorography. He demonstrated that the camera is much more effective than the eye in detailed recording of the image on a fluorescent screen.

Work in this field continued and refinements of technique such as larger lenses, mirror objectives, improved fluorescent screens, rapid-roll and finer grained films have appeared. *Janker* (1938), who had discussed related problems as early as 1926, described at a German roentgen congress in 1935 some improvements which permitted shorter exposures and a satisfactory distance between the tube and the screen.

In the following year, then, *de Abreu* began to examine large sections of the population with photofluorography. He used 35 mm film and the films obtained were 24 × 35 mm. After this beginning, large-scale surveys

were undertaken in many countries. In 1937 and 1938 Danish and British workers experimented with 35 mm fluorography and in the latter year *Johannes Holm* (1945) began systematic annual examination of medical students in Copenhagen. After a transportable apparatus had been constructed, a rapid mass survey of the population of Mecklenburg in Germany was carried out in 1939 under the leadership of *Holdfelder*. Between March and July of that year approximately 640,000 persons were examined. This study was reported by *Berner* (1939).

In Sweden, *Törnell* (1940) was the first to apply the method on a large scale. Like *Holdfelder*, he used 24 × 24 mm film. In 1941 mass radiographic examination of the Swedish army was begun by *Axén* (1941), and of the navy by *Nelson* (1946).

Under the auspices of the Swedish National Association against Tuberculosis, the first county-wide radiographic survey was carried out in 1943. On the island of Gotland 59,964 persons, comprising more than 99 per cent of the population, were examined.

Since then, all the counties of Sweden have been surveyed at least once. The first county-wide survey to be jointly financed by the State and the Local Authority was carried out in Södermanland County, commencing in 1946. The results are included in the present investigation.

2. *Swedish mass radiographic studies without prognostic investigation*

A measure of the need for radiographic surveys of a population in order to diagnose pulmonary tuberculosis at an early stage is the number of persons with advanced, cavitary lesions who are hospitalized for the first time for this disease. *Fürst* (1952) showed that at a Swedish sanatorium such cases during the period 1946 to 1950 comprised 29 per cent of first hospitalizations for postprimary tuberculosis of the lungs. This figure was lower than in earlier years, partly because of mass radiography of selected population groups; nevertheless, it demonstrated the necessity of a roentgenographic survey of the entire population served by the sanatorium.

Andén (1949) reported the results of a radiographic survey of the population of Uppsala County from 1945 to 1947, which was organized by the county medical authorities. Persons older than 2 years were eligible and in 2 towns 78.8 per cent and 96.8 per cent of the respective populations participated; the figure for the rest of the county was 97.0 per cent. From the total numbers of eligible persons had been subtracted those who had "truly valid reasons" for nonparticipation. The number of cases of active tuberculosis thereby discovered and previously unknown was 360, i.e., 2.9 per thousand examined persons.

Wegelius & Wijkström (1958) collected the results of several general population surveys during the years 1946 to 1956. Three regions had been surveyed twice during this period. The total of persons examined in the first-time surveys was about 3.9 million and 70 to 96.9 per cent of the eligible populations participated. In the repeat surveys the examined persons totalled about 724,000 and the participation rate ranged from 67.8 to 96.8 per cent. Newly discovered cases of intrathoracic tuberculosis which were notified as the result of the first group of surveys comprised 2.1 per thousand of the examined persons. In the repeat surveys this figure was 1.5 per thousand. In addition 4.4 and 2.2 per thousand of the examined persons were placed under observation for tuberculosis, but were not notified.

Wijkström & Wegelius (1953) pointed out that the demarcation between active and quiescent tuberculosis is indistinct in primary presentations and also that the percentage of non-notified observation cases varied greatly from survey to survey.

Detailed analysis of the primary results of mass radiography is not the intention of the present investigation. Prognostic findings in some mass surveys will therefore now be presented.

3. *Prognostic investigations of tuberculosis detected by mass radiography*

Following a mass survey of 44,072 persons in the Swedish navy in 1941 and 1942, *Nelson* (1946) reported a follow-up study of the cases with positive findings. The observation period was about 2 years. Printed questionnaires were sent out to tuberculosis dispensaries, sanatoriums, hospitals, and to the persons themselves.

Of the 1,209 persons concerned, 105 were not roentgenographically examined after mass survey. The results of post-survey roentgenograms were known in 1,020 cases. Of the 204 cases of active tuberculosis found at mass survey, 194 were traced after about 2 years: 52.0 per cent were then improved, the condition of 24.8 per cent was unchanged, 16.0 per cent were worse, and 6.2 per cent had died of tuberculosis. Of 227 cases initially regarded as inactive tuberculosis, 4.8 per cent were worse at follow-up and 1 was dead of tuberculosis. Also in the group of 494 persons originally classed as having healed tuberculosis there was 1 death from the disease and 1.6 per cent worsening.

The initial findings from mass radiographic survey of the island of Gotland were described by *Lundquist* in 1944. Of the examined population, 3.6 per thousand were notified as previously unknown cases of active pulmonary tuberculosis. The age distribution in these cases showed both ab-

solute and relative preponderance for persons older than 60, and *Lundquist* stressed the importance of elderly persons in this respect.

In an account of tuberculosis dispensary work on Gotland, *Nordgren* (1947) presented a report which may be regarded as prognostic information after 2 1/2 years of observation. The cases of active tuberculosis found as the result of the mass survey had then increased to 4.8 per thousand examined persons. Of these 270 cases, 19 had been removed from the register of tuberculous persons as recovered and 16 had left the island or had died of other causes than tuberculosis. Fourteen men and 7 women, totalling 7.8 per cent of the 270 cases, had died of tuberculosis; the mass survey films showed pulmonary cavitation in 11 of these men and in 4 of the women. About 80 per cent of the cases thus remained on the tuberculosis register.

Bidermann et al. (1946) described mass radiography during the period 1941 to 1943 of 56,541 employees of the French railways; about 80 per cent of the staff in the regions concerned were examined.

In addition to 422 cases already known, 7 of whom were found to have recurrence, 134 cases of pulmonary tuberculosis were discovered, including 129 with tests positive for tubercle bacilli. Cavitation was present in 73 of the new cases. At follow-up 2 to 4 1/2 years later, 12 cases were lost to observation. Death from tuberculosis had occurred in 19.7 per cent of the remaining 122 cases and 2.5 per cent were dead of other causes. Of the persons with positive bacillary findings at mass survey, 48 per cent were now at work.

In 279 further cases "pulmonary or pleural anomalies" necessitated observation. Forty cases could not be traced at follow-up and 40 had developed tuberculosis, with positive bacillary findings in 31 cases.

In the English city of Leeds, a mass radiographic survey of the general population was carried out from 1944 to 1946, and 40,753 apparently healthy persons were examined. *Aspin* (1949) reported the results in those who were residents of the city — about 34,000 with equal sex distribution. The percentage of participation was not stated.

"Evidence of unsuspected post-primary tuberculosis" was observed in 526 persons, of whom 293 were referred for observation (232 with minimal tuberculosis, 44 with moderately advanced and 17 with far advanced lesions). After at least 2 years of observation contact had been lost with 12 cases of minimal tuberculosis and 14 more were excluded because of inadequate follow-up. Of the original 526 with positive mass survey films, 436 were stated to have "remained healthy". The others were classified by *Aspin* as "sufferers", i.e., persons with roentgenographic and/or other signs of active tuberculosis. These 90 "sufferers" comprised 29 cases of minimal tuberculosis, all 44 cases of moderately advanced and all 17 of far

advanced tuberculosis. Of the patients with minimal tuberculosis, 2 died during the observation period, 8 became worse and 19 improved. The corresponding figures for the moderately advanced group were 11, 7 and 26 and for the far advanced cases they were 9, 1 and 7.

Caplan (1951) followed up cases of tuberculosis detected by mass radiographic study of the population of Trondheim in Norway during 1945 and 1946. About 36,000 persons, or c. 80 per cent of the population older than 15 years, were examined.

At the time of the survey, 127 persons were classed as being in need of care for tuberculosis and were notified. In addition, 510 required observation. All of the former group were available for follow-up study. After 5 years 28.3 per cent showed progression of the disease, 3.1 per cent were dead of tuberculosis and the same number of other causes. The remaining patients were fit for work.

Only 362 of the 510 observation cases could be followed up but in this group, too, there was evidence of active tuberculosis. Thus, in 31 cases there was roentgenographic progression of the lesions and 9 other patients were hospitalized for tuberculosis at the time of the report. Three had died of this disease. *Caplan* emphasized the difficulties in making a satisfactory diagnosis at the initial examination and concluded that apparently stationary lesions should be notified more frequently than was done in his series.

In 1946 a mass radiographic survey intended to cover the adult population of Muscogee County in Georgia, U. S. A. was undertaken. Although negroes constituted only about 30 per cent of the total population, 89 per cent of those over 15 years of age were reached by the survey, while only 51 per cent of the white population over 15 years participated (*Burke, Schenck & Thrash* 1949).

According to *Comstock & Sartwell* (1955), who published an evaluation of this survey on the basis of 6 years of observation, 38,190 persons were examined. At the time of the survey 712 films were considered to be positive; these included an unstated number from "persons with a previous diagnosis of tuberculosis". At the end of the 6-year observation period (1952), 144 cases had been discharged as nontuberculous. The remaining 568 were reclassified on the basis of findings *throughout* the observation period — roentgenograms, bacteriologic tests, tuberculin tests and clinical records — into the following groups: *Class I,* reserved for cases with positive bacteriologic findings (or, rarely, pathologic findings in the absence of positive sputum), *class II,* the "presumptive group", including those in which the roentgenographic findings were "reasonably consistent" with tuberculosis, and *class III,* "the suspects", comprising cases in which it was less certain that lesions were present, or in which the lesions were more

suggestive of a nontuberculous condition. Class I contained 114 cases, class II 249 and class III 205.

In *class I* (by definition the active cases of pulmonary tuberculosis) the white persons constituted 2.4 per thousand of the total white persons in the survey and the negroes comprised 3.8 per thousand of the examined negroes. In both races the frequency of tuberculosis was greater in persons of 45 and over than in younger persons, except in negro women, where the younger group predominated. Of the total groups initially selected for follow-up because of mass survey findings, 11.7 per cent of the whites and 23.9 per cent of the negroes showed definite signs of active tuberculosis. In a later paper, dealing with tuberculosis mortality during 7 years after the 1946 survey, *Comstock* (1956) reported the mortality in the survey-positive cases to be approximately 2.5 per cent for whites and 10 per cent for negroes.

Comstock & Sartwell wished to evaluate the morbidity from tuberculosis during a 6-year follow-up of all persons examined in a community-wide radiographic survey. Their difficulties were considerable, particularly as regards migration from the survey area. The value of their findings for comparison with those of other writers is diminished by the low participation rate and by the absence of tuberculosis classification made at the time of the survey. Moreover, as these writers stated, the examined persons were not representative of the population as regards race, sex or age distribution.

Another American study (from Erie County) was presented by *Ames & Schuck* (1953). It was based on cases notified following continuing mass radiography from March, 1946 to December, 1950. From 330,585 miniature films, 976 cases of "tuberculosis more active than apparently cured" were found. Excluded from the study were 320 of these cases; 57 per cent of them were already known to have tuberculosis and the remainder were disqualified because of nontuberculous lesions, nonresidence in the survey area, or insufficient follow-up. About 11 per cent of the excluded cases were lost to observation but were known to have become ill with pulmonary tuberculosis later. Of the 656 cases followed up only 37 were not white.

Classification was made immediately after the survey film and the first clinical examination. In 84.6 per cent of the cases the lesions were considered to be minimal, while in 14.0 per cent they were moderately advanced and in 0.6 per cent far advanced; in 0.8 per cent the stage was undetermined. As "active" tuberculosis were classed active or quiescent lesions, according to the 1940 NTA[1] definition. Such cases comprised 39.3

[1] National Tuberculosis Association, U. S. A.

per cent of the total 656 and were distributed as 27.1 per cent minimal tuberculosis, 11.6 moderately advanced and 0.6 per cent far advanced (i.e., all the far advanced cases).

The observation period ranged from 6 months to more than 5 years and averaged 2.7 years. At the end of observation 210 cases were classed as improved, 145 as stationary, and 114 as progressed, including 23 deaths from tuberculosis; 10 persons had died of other causes, 10 were lost to observation and 167 were well but their clinical status was undetermined. Fatal tuberculosis was about 3 times as common among the coloured as among the white patients.

Five of the deaths from tuberculosis occurred in cases which initially were not judged to be active.

Positive findings from mass radiography of the population of Washington, D.C. in 1948 were followed up by *Payne, Enterline & Heuck* (1952). Of the resident population 352,600, or 50 per cent of the eligible persons (15 years old and over) took part in the survey. Approximately 47 per cent of the eligible white population and 58 per cent of the non-whites were examined.

Among the residents, 2,776 persons were diagnosed as having previously unknown tuberculosis; 18 of these were less than 15 years old. The original classification of the lesions was minimal in 1,530 cases, moderately advanced in 439 and far advanced in 103. In 704 cases the classification was "suspected possible pathology and all other"; lack of bacteriologic aids to diagnosis and insufficient observation were suggested as causes of this diagnostic uncertainty. As "active" (including active, quiescent and questionably active) were classed 654 cases, and as "inactive" (including inactive, apparently arrested, arrested and apparently cured) 1,588 cases. In 534 cases the activity was not stated. This classification was also based on initial findings.

The cases were followed up for 2 years, and regarding deaths from tuberculosis for 2 1/2 years. The mortality rate for the cases originally considered to be "active" was 5.7 per cent. For all cases it was 2.5 per cent. Among the far advanced cases the tuberculosis mortality was 23.7 per cent.

The probability of progression in cases originally placed in the "inactive» group was almost 10 per cent.

It was calculated that at the end of the survey 65 per cent of the tuberculosis cases in the District residents were known. As earlier experience had shown, the proportion of known cases was less in the higher age groups — 39 per cent in those 55 years of age and over as compared with 79 per cent in the 15 to 54 year age group.

Brocard, Duplay & Le Du (1956), from a mass radiographic survey

of about 68,000 employees in private industries in 1952, found 810 cases of previously unknown pulmonary tuberculosis. These they initially classed into 3 groups. The first group comprised 498 persons with cicatricial lesions. The second contained 234 whose lesions were not of cicatricial structure or density, but who were considered to require only observation and not treatment. The third group was made up of 78 persons in need of treatment. In all groups there was a predominance of males, who formed 78 per cent of the total cases.

The period of observation ranged from 1 to 3 years. In group 2, to which the writers devoted most attention, 220 cases could be traced and of these 44 showed tuberculous progression. Concerning the results of treatment in mass-survey detected cases, these were stated to be better on the whole than in cases discovered following clinical symptoms, but the difference was not so great as might have been expected. No figures for mortality were given.

In London, *Springett* (1956) made special study of the prognosis of mass-survey detected minimal tuberculosis (NTA definition). Since the examined persons were mainly civil servants, post office workers, industrial workers and students and were 15 to 44 years of age, they were not representative of the general population. The examination was voluntary and it was estimated that about 50 per cent of the approached persons participated. Collection of volunteers began in January, 1946 and ended in April, 1948 for women and in October, 1948 for men. Accepted for study of minimal tuberculosis were 613 women, most of whom were between 20 and 34 years of age and 600 men, mainly in the 25 to 34 year age group. The selection of minimal tuberculosis was independent of the activity of the lesions. *Springett's* report is highly detailed and illustrates mass radiography from many aspects.

The period of follow-up was at least 5 years. In 105 of the original 1,213 cases the 5-year status was not known; 96 of these persons were not known to have received treatment for tuberculosis, 8 had defaulted from supervision after treatment and 1 had died of another cause during treatment for tuberculosis. Progression was observed during the 5-year period in 29.5 per cent of the patients; 13 per cent became worse in the first 6 months of observation and 9.5 per cent in the second 6 months. Some indication of activity had been shown by the end of 5 ½-years in about 40 per cent of the cases discovered by 1 of the 2 mass radiography units in the study, and in about 50 per cent of the cases from the other unit.

There were 3 deaths from tuberculosis and 6 from other causes. At the end of observation 60.7 per cent of the patients had lost no time from work because of tuberculosis, 27.0 per cent were at work after

treatment or with some form of pulmonary collapse, 5.4 per cent were unfit for work and receiving treatment, and in 6.2 per cent information was not available.

Among other studies of mass radiography which include prognostic data may be mentioned those of *Silverman* (1949) who followed up selected population groups in Baltimore, U. S. A. for a year or more, and *Meersseman* (1950) in France, who observed military personnel for 1 to 4 years.

A preliminary report regarding the prognosis of pulmonary tuberculosis diagnosed by mass radiography was read before the 18th Scandinavian Tuberculosis Congress in 1956 by *Källqvist & Hedin*. This report was based on the cases of pulmonary tuberculosis discovered by mass radiographic survey of Södermanland County from 1946 to 1948. The observation period was 6 to 8 years. As the clinical material has now been investigated from many more aspects and the follow-up period has been extended to 8 to 10 years, recapitulation of the 1956 report is superfluous.

Some relevant data from the most important of the investigations reviewed in the foregoing pages are presented in table 1.

4. *Prognostic comparison between mass-survey detected and "control" cases of tuberculosis*

Many of the cases of tuberculosis which are detected by mass radiography would otherwise proceed to a more advanced and symptomatic stage but, as pointed out by *Anderson, Enterline, Hill & Roberts* (1954), no one knows in the individual case what would have happened in the absence of survey examination.

These writers nevertheless attempted to estimate the value of mass radiography by comparing cases of active pulmonary tuberculosis which were discovered in a survey from May to August, 1947 with active tuberculosis found in the same area by other means during the first 6 months of 1947. Among about 261,000 survey-examined residents of Minneapolis, U. S. A., 135 were proved to have active pulmonary tuberculosis which was unknown prior to the survey. These were compared with 134 resident active cases of pulmonary tuberculosis which had been routinely reported to the city's Health Department. The minimum age in both groups was 15 years.

At the time of diagnosis far advanced tuberculosis was more common in the nonsurvey cases than in the survey group — 32.8 per cent and

TABLE 1. *Some Follow-up Studies of Mass-Survey Detected Pulmonary Tuberculosis*

Author(s), country, study period	Category and no. of participants[1]	No. of cases	Definition of cases
Nelson, Sweden 1941—42	Naval personnel 44,072	204 522 258	"active pulmonary tuberculosis" "healed pulmonary tuberculosis" "inactive pulmonary tuberculosis"
Nordgren, Sweden 1943	General population 56,964 (> 99 %)	270	"definitely active tuberculosis"
Bidermann et al. France 1941—43	Railway employees 56,541 (c. 80 %)	134 279	sputum positive and/or cavity "pulmonary or pleural anomalies necessitating phthisiologic supervision
Aspin, England 1944—46	General population c. 34,000	293	"unsuspected post-primary tuberculosis ..... referred for observation"
Caplan, Norway 1945—46	General population c. 36,000 (c. 80 %)	127 510	"in need of treatment" "in need of observation"
Comstock & Sartwell, U. S. A. 1946	General population 38,190 (c. 50 %)	568 (379 white, 189 non-white)	"survey films positive"
Ames & Schuck, U. S. A. 1946—50	General population 330,585	 258 398 (619 white, 37 non-white)	"clinically significant tuberculosis": "active" "other"
Payne, Enterline & Heuck U. S. A. 1948	General population 352,600 (c. 50 %)	654 1,588 534 (c. 2,000 white, c. 700 non-white)	"active, quiescent and questionably active" "inactive, apparently arrested, apparently cured" "activity not stated"

[1] per cent figures denote participants in per cent of population.

No. followed up	Period of follow-up	Results of follow-up	
		Deaths from tuberculosis (%)	Other findings (%)
194	c. 2 years	6.2	improved 52.0, unchanged 24.8, worse 16.0
494	» 2 »	0.2	unchanged 97.8, worse 1.6
227	» 2 »	0.4	unchanged 92.2, worse 4.8
c. 260	2½ years	7.8	removed from register, "cured" 7.0
122	2—4½ years	19.7	of 129 sputum-positive cases, 48 % fit for work
c. 240	"some months or years"		"manifestations of pulmonary tuberculosis" 13.7
267	⩾ 2 years	8.2	improved or no worse 19.5, worse 5.9 (90 patients selected as "sufferers", i. e., roentgenographic and/or other signs of active tuberculosis)
127	c. 5 years	3.1	fit for work 66.1, progression 28.3
362	» 5 »	0.8	progression 11.0 (including 2.5 in hospital)
⩽ 568 (no. lost to observation not stated)	⩽ 6 years	c. 2.5 white, c. 10.0 non-white (Comstock,' 1956)	apart from deaths, the initial and the final status are not separately presented
646	½—5 years (mean 2.7 years)	7.1 1.3 (c. 3 times as high among non-whites as among whites)	*Total followed up:* improved 32.5, stationary 22.4, well, status undetermined 25.9, progression 14.1
2,278	c. 2½ years	5.7 0.4 5.0	Tuberculosis deaths according to *extent* of lesions at mass survey: minimal . . . . 0.5 moderately advanced . . . 2.7 far advanced . . . . . . 23.7 (*activity* not shown correlated to *extent* of lesions)

15.6 per cent, respectively. The difference was also apparent as regards minimal tuberculosis — 37.0 per cent of the survey cases and 21.7 per cent of the controls. Moderately advanced tuberculosis, on the other hand, was similarly represented in the two groups — 47.4 per cent in the survey cases and 45.5 per cent in the controls.

The follow-up period was 4 years. At the end of that time 27 survey cases and 33 control cases were discharged from the investigation because they left the city, were considered uncooperative or were lost to observation. Eleven survey and 9 control cases were discharged as having arrested disease. Of the remaining 97 mass survey cases 13.4 per cent were dead. Among the 92 controls the death rate was 45.7 per cent. These figures referred to deaths from all causes; the tuberculosis mortality was not separately stated. Inactive tuberculosis, on the other hand, was more frequently present at follow-up in the survey cases (58.7 per cent) than in the controls (32.6 per cent). Tuberculosis was active in 27.8 per cent of the former group and in 21.7 per cent of the latter.

In Italy, *Giobbi, Calamari, Danese & Miradoli* (1956) compared 301 cases of tuberculosis discovered by mass radiography of the general population of Milan with 1,050 cases registered at the tuberculosis dispensaries following routine examinations or because of subjective or objective manifestations of the disease. Both groups derived from the period 1947 to 1950.

Five years later 83.0 per cent of the survey cases and 65.3 per cent of the controls were classed as recovered, 13.6 per cent of the survey group and 34.6 per cent of the controls were described as relapsing and 0.9 per cent of the former and 4.8 per cent of the latter as "chronics". Death from tuberculosis occurred in 1.6 per cent of the survey cases and 3.3 per cent of the controls. The frequency of relapse showed a gradual decline from 1947 to 1950, which was attributed to specific antimicrobial therapy.

Giobbi et al. also classified their cases according to whether the initial roentgenographic findings were bilateral or unilateral and cavitary or noncavitary. The frequency of relapse in the unilateral cases was 31.3 per cent among the controls and 19.6 per cent in the survey group. In the bilateral cases the corresponding figures were 45.7 and 18.5 per cent. Although the initial *activity* was not reported, the prognosis in all respects favoured mass-survey detected tuberculosis.

These two investigations concerned community-wide mass radiography. *Gomez & Piaggio* (1956) compared 232 cases of active tuberculosis discovered by systematic radiography of various population groups in Uruguay during 5 years from 1939 with a control series. This comprised 128 persons who, a short time — very often only weeks or months — after

group radiography had shown apparently healthy lungs, developed acute symptoms of pulmonary tuberculosis.

The observation period averaged 8 years. Deaths from tuberculosis then amounted to 12.3 per cent of the survey-detected cases and 27.3 per cent of the controls. In addition, 7.9 per cent of the former and 3.9 per cent of the latter had shown progression of the disease.

Gomez & Piaggio pointed out that some of the Uruguayan population had a low standard of living and were not BCG-vaccinated. In contrast to the survey-detected cases, the evolution of tuberculosis in the controls frequently was very rapid and serious. The writers also stressed that one must not equate minimal tuberculosis with early detected tuberculosis and assume that far advanced disease is the consequence of late diagnosis. Very often, they maintained, the advanced cases run an explosive course, and this they attributed to differences in the "soil", for the evolution of tuberculosis.

Fraser (1951) described the first 100 cases of tuberculosis admitted to an English sanatorium as the result of findings at mass radiography. These he compared with 100 cases also hospitalized for the first time but diagnosed by other means. The series were matched for time of admission and derived from the period 1943 to 1949.

These patients were followed up to December 31, 1949, so that the observation period ranged from less than 1 year to 7 years. No details were then available for 3 cases from each group. Of the remaining control cases 41.2 per cent were dead as compared with 8.2 per cent of those diagnosed by mass radiography. Active tuberculosis was present in similar proportion in both groups — 29.9 per cent in the mass survey cases and 28.9 per cent in the controls. Corresponding figures for cases classed as quiescent were 35.0 and 24.7 per cent and for arrested disease 26.8 and 5.1 per cent.

Only 1 case of the 100 in either group received specific medication. Collapse therapy was carried out in 57 of the mass survey cases and in 30 of the control cases. The mean age was 33 years in the former group and 37 in the latter. *Fraser* pointed out that the groups were not fully comparable. For instance, it was not known how many of the controls had been offered mass radiography, nor how many would have accepted such an offer. Neither was it known how many of the survey cases would have sought medical advice in the absence of mass radiography. Since tubercle bacilli were found in 82 of the survey cases, however, it was concluded that without mass radiography their disease sooner or later would have progressed until, when diagnosis was made, its severity approximated to that in the controls. The survey cases thus were younger than the controls, their tuberculosis was less advanced and more accessible to active treatment, and their prognosis was considerably better.

TABLE 2. *Some Follow-up Studies of Mass-Survey Detected Pulmonary Tuberculosis with Control Cases.*

Author(s) country, study period	No., category and definition of cases	No. followed up	Period of follow-up	Results of follow-up: Deaths from tuberculosis (%)	Results of follow-up: Other findings (%)
Anderson et al. U. S. A. 1947	*Mass survey* *135* cases of active tuberculosis from *general population*	97	4 years	$\leqslant$ 13.4	inactive tuberculosis 58.7; active » 27.8
	Controls *134* cases notified to Health Dept. for active tuberculosis (active = "positive bacterial findings or X-ray changes characteristic of tuberculosis")	92	4 »	$\leqslant$ 45.7 (figures refer to deaths from all causes)	inactive » 32.6; active » 21.7
Giobbi et al., Italy 1947—50	*Mass survey* *301* cases of tuberculosis from *general population*	$\leqslant$ 301	5 years	1.6	healed 83.0, relapsing 13.6, chronic 0.9
	Controls *1,050* cases of tuberculosis from routine dispensary work (initial activity of lesions not defined)	$\leqslant$ 1,050 (no. lost to observation not stated)	5 »	3.3	healed 65.3, relapsing 34.6, chronic 4.8
Gomez & Piaggio, Uruguay 1939—44	*Mass survey* *232* cases of active tuberculosis from *group examinations*	227	c. 8 years	12.3	regressive 77.5, stationary 2.2, progressive 7.9
	Controls *128* cases of active tuberculosis in persons with previous normal mass roentgenograms (very often only weeks or months before acute symptoms)	128	c. 8 »	27.3	regressive 68.0, stationary 0.8, progressive 3.9
Fraser, England 1943—49	*Mass survey* First *100* cases *hospitalized* following mass radiography	97	< 1—7 years	8.2	arrested 26.8, quiescent 35.0, active 29.9
	Controls *100* cases matched with above for time of diagnosis and hospitalization	97	< 1—7 »	41.2	arrested 5.1, quiescent 24.7, active 28.9

Courcoux, Bariéty & Courcy (1952) maintained, on the basis of findings from mass radiography in France, that the prognosis of tuberculosis was better when detected by this means than when spontaneously revealed. These writers, according to *Brocard et al.*, stated in 1952 at the 12th Conference of the International Union against Tuberculosis that, after the same observation time, 66 to 90 per cent of survey-detected tuberculosis cases had recovered, as compared with 50 to 66 per cent of other cases. *Babolini & Marconi* (1956) stated that pulmonary tuberculosis diagnosed by mass radiography could be cured on average in half the time required for cases found by routine dispensary work. They gave no figures, however.

The results of the first four of these comparative studies are briefly presented in table 2.

5. *Discussion*

The literature which has been reviewed in the preceding pages illustrates the difficulties of collecting representative clinical material for evaluation of the long-term prognosis of pulmonary tuberculosis detected by mass radiography. Community-wide surveys, in particular, are beset by the disadvantages of unsatisfactory participation rate and — most important — of incomplete follow-up. In Sweden the system of yearly population registration implies that all persons can be traced to a new place of residence. In countries lacking this system, persons who move away from the survey area are readily lost to observation.

Comparison between the various reports of mass radiography and follow-up is greatly hindered by lack of uniformity in the classifications and definitions used. Thus, known cases are not always separated from new cases, active and inactive tuberculosis may be presented in a single group, or racial complexity must be taken into account.

In the few investigations of prognosis with control cases of some type, the outlook was invariably better for tuberculosis detected by mass radiography. The difficulties, however, are to obtain a control series which, apart from the differences entailed by the method of diagnosis, is as satisfactorily matched with the survey cases as possible, to select suitable factors for comparison and to ensure adequate length of observation. When these conditions have been met, the survey participants must be representative of the population. My search of the literature has revealed no study which fulfils all these criteria.

CHAPTER II

PRINCIPLES FOR NOTIFICATION OF PULMONARY TUBERCULOSIS

A Swedish statute which came into force in 1940 made it obligatory to notify and register all cases of tuberculosis, excepting manifestly healed tuberculosis. This decree, therefore, determines whether or not a person with tuberculous pulmonary lesions shall be placed on the tuberculosis register. Even the most experienced phthisiologist, however, may find it difficult to decide without lengthy observation and detailed investigation if tuberculosis is manifestly healed. Where doubt exists, the patient may be placed under observation without being registered. Obviously, this borderline between cases to be notified and those only to be kept under observation may be variously interpreted by different examiners. A follow-up study, therefore, must not be confined to notified cases of tuberculosis; the fate of non-notified observation cases must also be investigated.

CHAPTER III

MASS RADIOGRAPHIC SURVEY 1946 TO 1948

1. *The tuberculosis situation at commencement of the survey*

The County of Södermanland is situated in the south-eastern part of central Sweden. It covers an area of 6,823 km^2 and has a population density of about 35 per km^2. When the first general survey with mass radiography was begun in 1946 the population of Södermanland was approximately 201,000 or 3 per cent of the total 6,674,000 Swedish population. In the continuing process of urbanization, the county has followed the tendencies in the country as a whole, and 58 per cent of the population lived in built-up areas. A root cause of this flight from the land was the well known displacement of labour from the falling needs of agriculture to developing industry and other occupations of towns. In Södermanland at the beginning of the mass radiography campaign 32 per cent of the population were engaged in or dependent on agricultural work. The figure for industry was 45 per cent and for other occupations 23 per cent. Corresponding figures for the country as a whole were 30, 40 and 30 per cent (*Holm* 1956).

The frequency of tuberculosis in Sweden since 1940 has been well charted, thanks to the decree making notification compulsory for all tuberculosis unless manifestly healed. Immediately before the first radiographic survey of Södermanland's population was begun, i.e. on December 31, 1945, the Swedish register of pulmonary tuberculosis showed 59,200 cases, or 8.9 per thousand of the population. In Södermanland 813 cases of pulmonary tuberculosis were registered, constituting 4.1 per thousand of the population. The number of notifications made during 1945 was 9,638 in the whole of Sweden (1.45 per thousand population) and 156 in Södermanland (0.8 per thousand). The age distribution of these new cases in the country as a whole is not known. On the other hand, patients discharged during 1945 following first hospitalization for intrathoracic tuberculosis are grouped according to age. Since almost all of these patients presumably had tuberculosis of the lungs, their ages may be used as a measure of the age distribution of the new cases of this disease at the time in question, with some reservation for the fact that lack of beds to some extent prevented admission of elderly persons. In figure 1 the numbers of these hospitalized persons are shown in relation to the respective age groups in the general population.

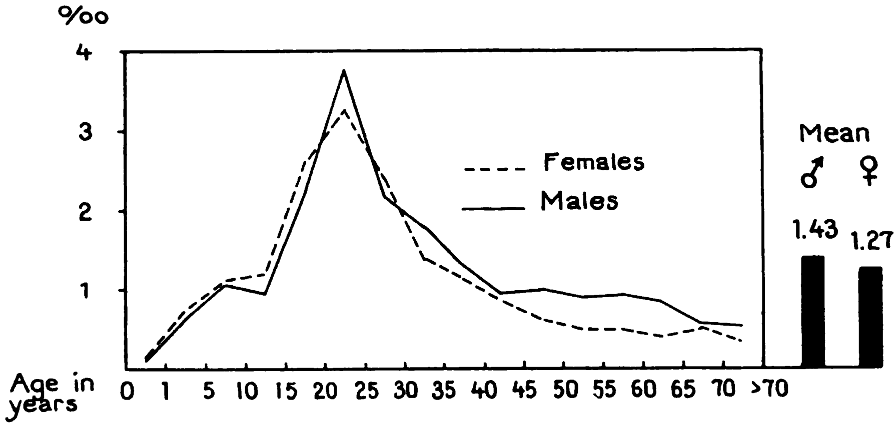


Fig. 1. **Age of patients discharged during 1945 in Sweden from first hospitalization for intrathoracic tuberculosis (in ‰ of age groups in Swedish population).**

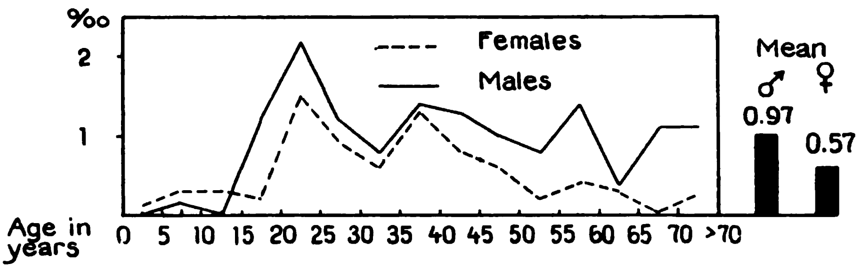


Fig. 2. **Age of patients notified during 1945 in Södermanland as having pulmonary tuberculosis (in ‰ of age groups in Södermanland's population).**

In Södermanland County the *newly detected* cases of tuberculosis in 1945 could be grouped according to age. Figure 2 shows these cases per thousand of their age groups in the county population.

Deaths from pulmonary tuberculosis in 1945 amounted to 0.57 per thousand population in the whole of Sweden and to 0.43 per thousand in Södermanland County.

Mortality and morbidity from tuberculosis had long been declining. Both affected primarily the age group 20 to 24 years in Sweden as well as in Södermanland.

2. *Method and participation rate*

The first mass radiographic study of Södermanland County took place from October, 1946 tó January, 1949. Persons who were examined in the group surveys of industrial workers which began in January, 1946 were also considered to have participated in the general survey, however, and were exempted from attendance at it.

Examination was voluntary and was intended to cover the entire population from school entrance age, i.e., from 7 years. The number of persons invited to attend was 178,344. This figure is exclusive of 2,281 persons who died or left the county before being reached by the survey and 246 men who were temporarily resident elsewhere in the course of military service and were examined in that connection. Included are the 10,204 industrial workers referred to above, who were examined immediately before the county-wide survey was begun, and also 1,425 mentally ill or deficient persons hospitalized in Södermanland.

Two circuits of the county were made. The second, which took place in the last 3 months of the survey, was intended to permit attendance of persons who hade not responded to the first call to examination.

The number of persons examined was 172,459, i.e., 96.7 per cent of those invited to participate, with 93.4 per cent in the first circuit and 3.3 per cent in the second. Of the 5,885 persons who were not examined, 3,552 were considered to have valid reasons for nonattendance and 2,333 (1.3 per cent) to have defaulted without valid reason. The first group of nonparticipants included persons who were immobile due to illness or other causes or who were temporarily resident outside Södermanland. The second group comprised persons who, with or without stating their reasons, declined to be examined. Double counting of persons who were examined more than once was precluded by collecting all the records at the county's only central tuberculosis dispensary and filing them according to date of birth.

For the high participation rate in this voluntary campaign credit is due to good organization and appropriate propaganda, which included home visiting by selected members of the local committees which were organized to assist the survey. Highly important were also, of course, the interest and support given by the general public.

Interpretation of the photofluorograms: The preliminary appraisal of the films (80 × 80 mm) was made at the Royal Medical Board's Mass Radiography Centre in Stockholm. To reduce the risk of error, the number of films examined daily by each reviewer was limited. In addition, dual reading was practised to some extent. From the Centre 5,667 photofluorograms were referred to the central tuberculosis dispensary in Söderman-

land for further assessment or investigation. There the cases already known to the dispensary, whether registered or nonregistered, were sorted out, as were also cases in which further investigation was deemed unnecessary.

3. *The positive findings*

At the Royal Medical Board's Mass Radiography Centre 13,905 photofluorograms were reported to show healed intrathoracic tuberculosis. Table 3, which is taken from the original account of the survey, shows the findings at the tuberculosis dispensary in Södermanland as regards the 5,667 films referred there for further evaluation. This account was published by *Mascher* (1949), who directed the survey, only a few months after the latter was terminated.

In his report, *Mascher* made the following primary classification of the cases which were in need of further observation.

a) *Hospital cases* = registered pulmonary tuberculosis requiring immediate sanatorium care.

b) *Notifiable observation cases* = manifest pulmonary tuberculosis, but not requiring hospitalization. In this group, however, were included a few persons with active tuberculosis, most of them elderly, who were considered unsuitable for active therapy and whose living conditions entailed only minimal risk of spreading infection.

c) *Non-notifiable observation cases* = lesions suspected to be tuberculous, or tuberculous lesions to be kept under observation but not placed on the tuberculosis register.

In addition to the totals stated by *Mascher* for these three groups, there were 44 persons (table 3) whose photofluorograms made further observation advisable, but who at the time of the 1949 report had not responded to requests for clinical examination.Thirteen of these cases were notified, however.

In the present investigation the cases are divided into two groups only, viz., *notifiable* and *non-notifiable* cases (for definitions, see p. 22). The 44 cases without clinical follow-through in *Mascher's* report have now been distributed in these two groups, according to the original evaluation.

4. *Discussion*

Södermanland County is one of the most favoured of the Swedish counties as regards tuberculosis. This is reflected in figures for morbidity and mortality.

TABLE 3[1]. *Suspected or Definitely Pathologic Mass Survey Films*
(Results of follow-through investigation)

	No. of cases	% of mass survey suspects	% of mass survey participants
Further tuberculosis observation not required:			
No pathologic findings	1,150	20.3	0.67
Healed tuberculosis	1,373	24.2	0.8
Nontuberculous conditions	1,321	23.3	0.76
Tuberculin-negative	188	3.3	0.1
Further tuberculosis observation required:			
Cases already known (registered or non-registered)	661	11.7	0.39
Non-notifiable observation cases	242	4.3	0.14
Notifiable tuberculosis — observation cases (including 10 nonpulmonary) . .	495	8.7	0.29
Notifiable tuberculosis — hospital cases .	193	3.4	0.11
Declined examination, not at home, etc.	44	0.8	0.02

[1] From *Mascher,* 1949.

Before the county-wide survey in Södermanland, only one other Swedish county had completed a mass radiography campaign. This was Gotland which, with its population of about 60,000, reached an attendance rate of more than 99 per cent. Since more than three times as many people were eligible for examination in Södermanland and participation was voluntary (as also in Gotland and subsequently throughout Sweden), the 96.7 per cent response in Södermanland must be regarded as highly satisfactory. It has been exceeded only once in later surveys in other counties.

For the original report of 1949 *(Mascher)* much effort was expended in classifying the individual cases on the basis of detailed clinical investigation. Bacteriologic studies were also well provided for, as gastric lavage could be done at all regional tuberculosis dispensaries in the county.

From several aspects it proved advantageous to retain the original classification of the case material, with the modification that all notified cases of pulmonary tuberculosis were placed in a single group.

CHAPTER IV

MASS-SURVEY DETECTED TUBERCULOSIS AND CONTROL SERIES 1946—1948

1. *General aspects*

By the above-mentioned combination into a single group of all cases of pulmonary tuberculosis which were notified directly after mass survey, the following classification was obtained.

a) *Notifiable cases* = persons with pulmonary tuberculosis who were initially placed on the tuberculosis register. This group includes all who were in need of hospitalization at diagnosis, irrespective of age and other circumstances, and whether or not hospitalization was given.

b) *Non-notifiable cases* = persons suspected or considered to have pulmonary tuberculosis who were placed under regular supervision but were not entered in the register of tuberculous persons.

The control material contained only persons initially registered as having pulmonary tuberculosis and the principles for registration were the same as in the survey cases.

In the survey cases and in the controls I have personally reviewed all the series of roentgenograms taken after diagnosis of the lesions, and also any earlier films which were available. For a few patients who had moved away from Södermanland County, however, the reports concerning follow-up status were provided by physicians at other sanatoriums or tuberculosis dispensaries.

The follow-up period extended to January, 1957 and both series thus were observed for at least 8 and at most c. 10 years. However, the patients who were freed from supervision during this period as no longer requiring such care were not followed up after this decision. Nor was investigation made concerning the fate of the few patients who emigrated from Sweden.

All the surviving patients who had not been freed from supervision were definitely traced at follow-up.

In each case in the study the data collected — up to 70 per person — were entered on a punch card. A comprehensive code system was used. Information desired was then obtained by mechanical sorting of the cards at the Central Bureau of Statistics in Stockholm.

2. *The mass survey cases*

In my review of tuberculosis diagnosed following mass radiographic survey I found it advisable to correct the basic figures given in table 3 for total numbers of notifiable and non-notifiable cases which required further observation. The following figures show the corrections made in the notifiable cases.

Report	**No. in report**	**Excluding**	**Including**
Mascher 1949	678	12 cases found by mass survey but "missed" in report 13 initially not available for follow-up (see table 3).	The 27 cases excluded by *Källqvist* (1958)
Källqvist & Hedin 1956	678	25 cases as above	27 cases as above
Källqvist 1958	676	10 cases with pneumoconiosis 12 with other, nontuberculous disease 5 cases later found to be already known	The 25 cases excluded by *Mascher* (1949)

In addition to the 10 notifiable cases with pneumoconiosis there were 2 among the non-notifiable group. Of these 12 persons, 10 showed no definite signs of active tuberculosis throughout the observation period. So as not to introduce unnecessarily the complicating factor of pneumoconiosis, I have excluded these 12 cases from investigation of prognosis.

In the mass survey group there remained 676 persons who were initially registered as having pulmonary tuberculosis and 275 who were not initially registered.

3. *The control cases*

For comparison with the survey cases I used a series of persons with pulmonary tuberculosis diagnosed by other means than the county-wide mass radiographic survey. These controls were taken from cases consecutively notified to the central tuberculosis dispensary between January, 1946 and January, 1949 — the time during which the survey cases were detected. For inclusion in the control series, however, the diagnosis had to be made *before* the mass survey reached the person's place of residence. A few persons were included who were under dispensary supervision before registration, but only if this supervision had been undertaken for conditions other than pulmonary tuberculosis, or for tuberculosis in the environment. The lower age limit in the controls, as in the survey cases, was 7 years.

The number of consecutively diagnosed persons who satisfied these criteria was 300. Six of them were found after observation to be free from pulmonary tuberculosis and were removed from the group. In two other cases pneumoconiosis complicated bacteriologically positive pulmonary tuberculosis: These were also excluded, for the reason stated in connection with pneumoconiosis in the mass survey.

In the control group there remained 292 persons, all of them initially registered as having pulmonary tuberculosis.

4. *The registered cases distributed according to year of diagnosis*

Table 4 shows that most of the mass survey cases were discovered in the years 1947 and 1948, whereas most of the controls were diagnosed in 1946 and 1947. With the conditions for inclusion in the control series, this distribution was to be expected.

The question then arises if the improvement in the tuberculosis situation, which in Sweden was expressed in *inter alia* a slow reduction of notifications and a much more abrupt decrease in deaths from tuberculosis, might have influenced the prognosis differently in the two series of cases. The county-wide mass radiographic survey resulted in a sudden increase of tuberculosis notifications (fig. 3), so that the annual notification rates cannot be taken to indicate morbidity trends. A better basis for study of a possible "natural" morbidity trend is provided by the control cases, since they were discovered independently of the mass survey.

In figure 4 is shown the population from which the control series was collected following deduction of persons examined in the mass survey. Thus, during the first trimester of 1946 the population available for control cases (= not reached by mass radiography) was on average 176,633 persons. For each subsequent trimester this total decreased at the same rate as the mass survey progressed. Correlation of the active cases of tuberculosis found during each trimester to the population not then reached by the survey gave the ratios stated above the diagram as "B in $^{0}/_{00}$ of A". These figures do not show any clear morbidity trend during the three years of the survey.

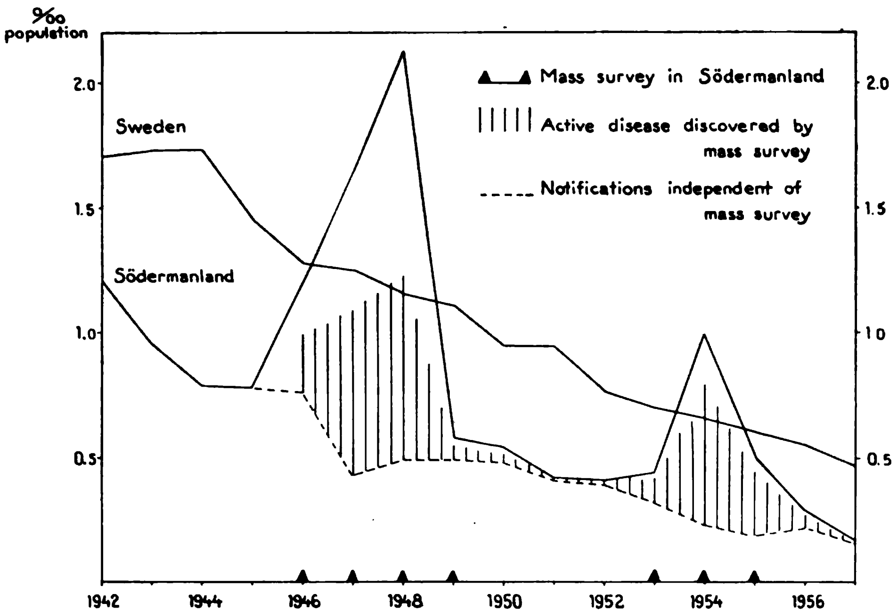
Deaths from tuberculosis in Södermanland County amounted to 74 in 1946, 60 in 1947 and 62 in 1948, constituting 0.37, 0.29 and 0.29 per thousand of the population in the respective years. Corresponding death rates for Sweden as a whole were 0.45, 0.44 and 0.35 per thousand.

Even if trends could be demonstrated in the general population as regards morbidity or mortality from pulmonary tuberculosis, they would not be relevant to my investigation, which concerns only newly detected

TABLE 4. *Year of Diagnosis in Notified Cases of Pulmonary Tuberculosis*

Year	Mass survey						Controls					
	Males		Females		Total		Males		Females		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1946	44	12.5	40	12.4	84	12.4	77	52.4	69	47.6	146	50.0
1947	136	38.6	107	33.0	243	35.9	42	28.6	56	38.6	98	33.6
1948	167	47.5	172	53.1	339	50.2	27	18.4	20	13.8	47	16.1
1949	5	1.4	5	1.5	10	1.5	1	0.7			1	0.3
Total	352		324		676		147		145		292	

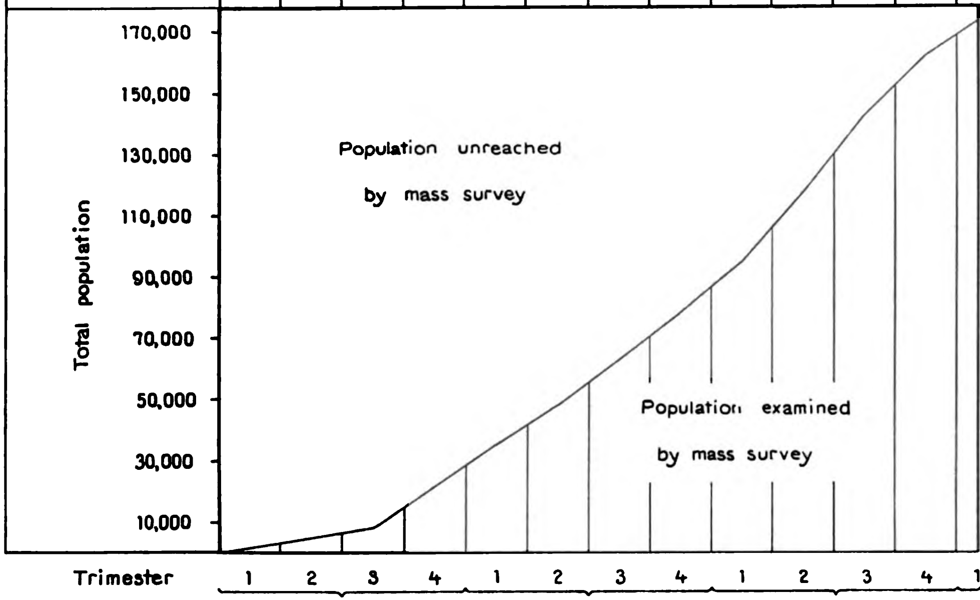
cases. The factors that influence the course of a disease are how advanced it is at diagnosis and how it is treated, rather than the year of diagnosis. It is such factors that have been taken into consideration in assessing prognostic results.



The figures for Sweden comprise *only* Swedish citizens. Therefore all figures for Södermanland are also limited to such persons.

Fig. 3. **Notifications of pulmonary tuberculosis in Sweden and Södermanland County 1942 to 1957.**

A. No. not reached by mass survey	176,633	173,791	169,792	156,624	142,566	131,056	116,507	100,702	83,634	60,959	35,816	16,769	7,489	5,885 persons no mass survey
B. No. of active controls found	35	41	26	25	14	33	19	14	16	11	7	6	1	
B in o/oo of A	0.20	0.24	0.15	0.16	0.10	0.25	0.16	0.14	0.19	0.18	0.19	0.36	See note	



Note: Value not calculated, as this period comprised only 24 days

Fig. 4. **Population (≦ 7 years old) available for mass survey and control cases in Södermanland.**

5. *Discussion*

That the initial assessment of all the cases in this study was made by the same physicians and during the same period of time constitutes a good guarantee of uniformity in the principles for the primary registration of tuberculosis discovered by mass radiographic survey and by other means. In my review of the clinical material I have personally assessed all data of importance for the investigation, in most cases without foreknowledge of the method of diagnosis. Consequently, this retrospective evaluation may also be considered to satisfy strict criteria of objectiveness and uniformity.

Mechanical treatment of the collected data permitted investigations of an extent which could not reasonably have been undertaken with a manual method. The punch-card system used and the centralized sorting conferred additional reliability.

Although the mass survey series and the controls were diagnosed during the same three-year period, they were dissimilarly distributed as regards year of diagnosis. But the change in the tuberculosis situation which has long been in process, and which has accelerated in the past decade, can scarcely be studied during the short time from which the cases derived and, having regard to the statistical method used, may be assumed not to have influenced the results of the study.

CHAPTER V

COMPARATIVE ANALYSIS OF REGISTERED MASS SURVEY AND CONTROL CASES

In order to ensure a similar basis for comparison between cases of pulmonary tuberculosis discovered by mass radiography and control cases, the non-notifiable cases are excluded from this chapter. They are separately presented in chapter XI. By notification and registration which, as already mentioned, were carried out by the same physicians during the same period of time, basic comparability was obtained between the registered mass survey cases and the control series. The cases which were not initially registered, on the other hand, formed a group whose heterogeneity from the outset was self-evident.

1. *Initial activity of tuberculosis*[1]

As stated on page 16, evaluation of activity made in close association with diagnosis of the tuberculous condition is of limited value for a clinical series as a whole. Only after investigation with the aids which are appropriate in the individual cases can more reliable judgement be made. In this study the activity of the tuberculous lesions at the time of diagnosis in each case was evaluated retrospectively at the end of the stated observation period (p. 22). Despite this, it was not possible to classify all cases as definitely active or definitely inactive.

The following were the criteria for the five classes of activity employed in the study.

I *Initially active:* Tubercle bacilli and/or cavitary lesions were demonstrated in most cases. In the other cases of the group there was progression or pronounced regression soon after diagnosis. When the only change was extremely slow shrinkage over a period of years, however, the case was not classed as active; such regression was regarded as indicating a parenchymal lesion of doubtful activity. This is in conformity with the definitions in the 1955 edition of "Diagnostic Standards and Classification of Tuberculosis" (NTA).

[1] "Initial" here refers to the time of diagnosis by mass radiography or other means.

II *Inactive: a)* The lesions appeared healed on serial roentgenograms and remained stable for at least 5 years. (According to the instructions by the Royal Medical Board a case may not be removed from the tuberculosis register until 5 years after the latest evidence of activity). In cases in which pre-registration films became available, this 5-year period could lie partly or wholly before the date of registration. *b)* Although the observation period was less than 5 years the lesions were regarded as manifestly healed. A condition, however, was that healing should be borne out by the roentgenographic appearance (mainly calcified lesions) or by autopsy findings.

III *Probably active:* These cases did not meet the requirements for "activity", but from their roentgenograms active tuberculosis should be suspected and other findings did not contradict this assumption.

IV *Probably inactive:* The serial roentgenograms showed stable lesions, but the appearance of these lesions did not convince that they were healed at the time of registration, or the observation period of apparently healed lesions was not long enough for classification as "inactive". The other findings did not contraindicate this classification.

To these four groups all the cases could be consigned, and this was also done.

V *Initially not active, later active:* There was, however, a category of cases which occupied a special position, viz., cases which the retrospective review showed to have had "non-active" tuberculosis (groups II to IV) at diagnosis, but which subsequently displayed activity. This progression was not directly associated with diagnosis. Group V is specially discussed in chapter IX. The designation "later active", like those of the groups from which the cases were extracted, contains a prognostic factor by virtue of the retrospective evaluation of initial activity.

2. *Roentgenologic classification according to extent of pulmonary lesions*

A prognostic comparison in pulmonary tuberculosis demands, in addition to evaluation of activity, roentgenologic differentiation of the cases according to the extent of the lesions. The most commonly used classification of pulmonary tuberculosis is that published by the National Tuberculosis Association (NTA) of America. In the 1955 edition of "Diagnostic Standards and Classification of Tuberculosis" we read:

»*Extent of Pulmonary Lesions*

Minimal. Slight lesions without demonstrated excavation confined to a small part of one or both lungs. The total extent of the lesions, regardless of distribution, shall not exceed the equivalent of the volume of lung tissue which lies above

the second chondrosternal junction and the spine of the fourth or body of the fifth thoracic vertebra on one side.

Moderately advanced. One or both lungs may be involved, but the total extent of the lesions shall not exceed the following limits:

Slight disseminated lesions which may extend through not more than the volume of one lung or the equivalent in both lungs.

Dense and confluent lesions which may extend through not more than the equivalent of one-third the volume of one lung.

Total diameter of cavities less than 4 cm.

Far advanced. Lesions more extensive than moderately advanced.»

This classification, however, permits fairly wide variations in type of pulmonary tuberculosis within each of the three groups. As regards *minimal* lesions, such large differences in frequency of occurrence have been reported from similar investigations that one may assume that the borderline between minimal and more advanced tuberculosis has not always received the same interpretation. *Springett* (1956) also pointed out the considerable variation which is possible within the definition of minimal tuberculosis. In my opinion, the NTA classification is open to the interpretation that dense and/or confluent lesions may be grouped under *moderately advanced,* even when they do not exceed the limits of extent set for minimal tuberculosis. In a personal communication, Dr *Julius Wilson* of the American Trudeau Society stated to me, however, that "the definition is one of extent and presence of cavitation, *without reference to the nature of the lesion.* Questions of density and whether the lesions are discrete or not do not enter into the definition." The *moderately advanced* and *far advanced* groups permit differentiation according to, for instance, presence or absence of cavity.

I have therefore subdivided all three NTA groups. The factors determining the character of the subgroups were presence or absence of excavation, total diameter of cavity or cavities, and whether the lesions were unilateral or bilateral. The details are schematically illustrated in table 5.

Minimal tuberculosis, as shown in table 5, was divided into 2 main groups. *Minimal I* comprised one or a few small, well-defined and discrete parenchymal densities, each measuring less than 1 cm^3 (subgroups A and B in table 5). *Minimal II* consisted of larger densities or of confluent lesions (C to F). Special subgroups of minimal II were noncalcified primary lesions (E) and coin lesions at least 1 cm in diameter (F).

Moderately advanced tuberculosis was subdivided into cases without excavation (G to J) or with excavation (K to O). G and H comprised scattered, small lesions and I and J denoted dense and confluent lesions. The cavitary cases were distributed according to total cavity diameter, viz., less than 2 cm (K and L) and at least 2 but smaller than 4 cm (M to O).

In certain comparisons the noncavitary subgroups were classed together

as *moderately advanced I,* and the cavitary cases were called *moderately advanced II.*

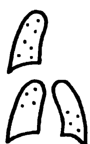
In *far advanced tuberculosis* the subgroups P and Q included cases without manifest excavation as well as cases with single or multiple cavities whose total diameter did not reach 4 cm. All the cases in subgroups R, S and T had cavity or cavities measuring 4 cm or more in total diameter. P och Q are not further subdivided in table 5 according to presence or absence of cavitation, mainly because in such large and confluent parenchymal densities small cavities cannot always be detected without the assistance of roentgenographic techniques finer than those in routine use, and which at the time of the mass radiographic survey generally were not employed unless their information could influence therapeutic decisions.

Also the far advanced cases were for some comparisons collected into 2 groups, viz., *far advanced I* comprising lesions without demonstrated cavity, or cases with cavity or cavities less than 4 cm in total diameter, and *far advanced II,* the remaining cavitary cases. In this latter group were placed the 5 persons without roentgenograms (subgroup U in table 5) but with such advanced, bacteriologically positive pulmonary tuberculosis that they died at home soon after diagnosis and before roentgenographic examination could be undertaken.

Roentgenographic examination thus was carried out in association with registration in all but the above-mentioned 5 control cases. In addition to postero-anterior views at least one other projection, such as oblique or lateral, was used in almost all cases. Tomography was carried out to some extent. These films and all later roentgenograms were, as already stated, with very few exceptions reviewed by me, thus ensuring uniformity of evaluation.

Table 5 presents all the registered cases in detailed subgrouping (A to U) and ends with the 4 main groups of the modified NTA classification, including 2 classes of minimal tuberculosis. To the left in the table are shown the complete mass survey series of registered cases and the complete controls, and to the right only those in which the lesions were initially active. It is seen that the control series contained more advanced tuberculosis than did the survey series as regards both total cases and active cases. Thus, 67.1 per cent of the controls were moderately advanced or far advanced, but only 49.2 per cent of the survey cases were in these categories. Among the initially active cases *72.9* per cent of the control group and *59.3* per cent of the survey group were moderately or far advanced. The difference was greater still if far advanced tuberculosis is considered alone — 35.6 per cent of all controls and 10.3 per cent of all survey cases, and *41.1* per cent of initially active controls and *17.1* per cent of initially active survey cases. This was to be expected, of course, as

TABLE 5. *Distribution of Material according to Modified NTA Classification*

Modified NTA groups		All cases											
		Mass survey						Controls					
		Males		Females		Males plus females		Males		Females		Males plus females	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
		Minimal I											
A		63	17.9	70	21.6	133	19.7	7	4.8	22	15.2	29	9.9
B		31	8.8	38	11.7	69	10.2	8	5.4	8	5.5	16	5.5
		Minimal II											
C		51	14.5	40	12.4	91	13.5	10	6.8	14	9.6	24	8.2
D		11	3.1	23	7.1	34	5.0	5	3.4	3	2.1	8	2.7
E	Primary tuberculosis	3	0.8	8	2.5	11	1.6	8	5.4	11	7.6	19	6.5
F	Tuberculoma	1	0.3	4	1.2	5	0.7						
		Moderately advanced											
G		5	1.4	5	1.5	10	1.4	1	0.7	1	0.7	2	0.7
H		11	3.1	13	4.0	24	3.5	4	2.7	5	3.4	9	3.1
I		41	11.6	29	8.9	70	10.4	10	6.8	8	5.5	18	6.2
J		69	19.6	54	16.7	123	18.2	15	10.2	8	5.5	23	7.9

Initially active lesions												Groups
Mass survey						Controls						
Males		Females		Males plus females		Males		Females		Males plus females		
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Minimal I												
17	9.9	26	15.5	43	12.7	6	4.8	13	10.7	19	7.7	A
5	2.9	12	7.1	17	5.0	2	1.6	4	3.3	6	2.4	B
Minimal II												
23	13.4	27	16.1	50	14.8	6	4.8	11	9.0	17	6.8	C
4	2.3	13	7.7	17	5.0	3	2.4	3	2.5	6	2.4	D
3	1.7	6	3.6	9	2.7	8	6.3	11	9.0	19	7.7	E
1	0.6	1	0.6	2	0.6							F
Moderately advanced												
2	1.2	2	1.2	4	1.2	1	0.8	1	0.8	2	0.8	G
4	2.3	3	1.8	7	2.1	2	1.6	3	2.5	5	2.0	H
20	11.7	18	10.7	38	11.2	9	7.1	6	4.9	15	6.0	I
33	19.3	25	14.9	58	17.1	12	9.5	5	4.1	17	6.9	J

Table 5. *(cont'd)*

Modified NTA groups		All cases											
		Mass survey						Controls					
		Males		Females		Males plus females		Males		Females		Males plus females	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
		Moderately advanced (cont'd)											
K		14	4.0	3	0.9	17	2.5	9	6.1	9	6.2	18	6.2
L		4	1.1	5	1.5	9	1.3	5	3.4	2	1.4	7	2.4
M		5	1.4	2	0.6	7	1.0	5	3.4	6	4.1	11	3.8
N		3	0.8			3	0.4	2	1.4	1	0.7	3	1.0
O								1	0.7			1	0.3
		Far advanced											
P		8	2.3	6	1.8	14	2.1	6	4.1	6	4.1	12	4.1
Q		24	6.8	18	5.5	42	6.2	26	17.7	16	11.0	42	14.4
R		2	0.6	1	0.3	3	0.4	8	5.4	6	4.1	14	4.8
S		6	1.7	3	0.9	9	1.3	11	7.5	10	6.9	21	7.2
T				2	0.6	2	0.3	5	3.4	5	3.4	10	3.4
U	No roentgenogram							1	0.7	4	2.8	5	1.7
		Total											
Minimal I		94	26.7	108	33.3	202	29.9	15	10.2	30	20.7	45	15.4
Minimal II		66	18.7	75	23.1	141	20.9	23	15.6	28	19.3	51	17.5
Mod. advanced . . .		152	43.2	111	34.2	263	38.9	52	35.4	40	27.6	92	31.5
Far advanced		40	11.4	30	9.3	70	10.3	57	38.8	47	32.4	104	35.6
Total		352		324		676		147		145		292	

Initially active lesions												Groups
Mass survey						Controls						
Males		Females		Males plus females		Males		Females		Males plus females		
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Moderately advanced (cont'd)												
14	8.2	3	1.8	17	5.0	9	7.1	9	7.4	18	7.3	K
4	2.3	5	3.0	9	2.7	5	4.0	2	1.6	7	2.8	L
5	2.9	2	1.2	7	2.1	5	4.0	6	4.9	11	4.4	M
3	1.7			3	0.9	2	1.6	1	0.8	3	1.2	N
						1	0.8			1	0.4	O
Far advanced												
6	3.5	4	2.4	10	2.9	5	4.0	6	4.9	11	4.4	P
19	11.1	15	8.9	34	10.0	25	19.8	16	13.1	41	16.6	Q
2	1.2	1	0.6	3	0.9	8	6.3	6	4.9	14	5.6	R
6	3.5	3	1.8	9	2.7	11	8.7	10	8.2	21	8.5	S
		2	1.2	2	0.6	5	4.0	5	4.1	10	4.0	T
						1	0.8	4	3.3	5	2.0	U
Total												
22	12.9	38	22.6	60	17.7	8	6.3	17	13.9	25	10.1	
31	18.1	47	28.0	78	23.0	17	13.5	25	20.5	42	16.9	
85	49.7	58	34.5	143	42.2	46	36.5	33	27.1	79	31.8	
33	19.3	25	14.9	58	17.1	55	43.7	47	38.5	102	41.1	
171		168		339		126		122		248		

the primary reason why the majority of the controls were registered was that symptoms caused them to seek medical advice.

In minimal I and minimal II tuberculosis and in the cavitary moderately advanced cases unilateral lesions were more common than bilateral. In far advanced tuberculosis and in the noncavitary moderately advanced cases bilateral lesions predominated. This distribution was almost without exception found in both sexes, in the total mass survey series and the total controls, and in the active cases of each series.

Strict classification according to presence or absence of cavity was not possible in all cases, as the far advanced subgroups P och Q, which comprised *12.9* per cent of the initially active mass survey cases and *21.0* per cent of the active controls contained, for the reasons already stated, cases with and cases without manifest excavation. The frequency of verified cavitation in these groups (P plus Q), however, was 20 of 44 (*45* per cent) in the mass survey series; 8 of the 20 were men. The corresponding figures for the control cases were 27 of 52 (*52* per cent) and 15 men.

Excavation thus was seen in 10 per cent of the total registered mass survey series and in 38 per cent of the total controls. Among the initially active cases, *21* per cent of the survey series and *45* per cent of the controls were found to have cavitary lesions.

This classification into 20 subgroups permits a clear survey over the composition of the two series of cases. Some of the subgroups were very small, however, and for this reason the usual NTA classification, with some exceptions, will be used in the following pages. The exceptions concern mainly minimal tuberculosis, which is divided into two groups.

3. *Correlation of initial activity to roentgenographic extent of lesions*

In figure 5 the initial activity of the lesions is shown in relation to their roentgenographic extent. The percentage of active cases increased with the extent of the disease. That the inactive cases were more numerous in the mass survey series than in the controls was to be expected, and also that in both series the inactive cases decreased as the tuberculosis became more extensive. One sees how minimal II tuberculosis resembles moderately advanced rather than minimal I as regards initial activity, thus supporting the advisability of in some respects dividing up "minimal" tuberculosis according to the principles I employed.

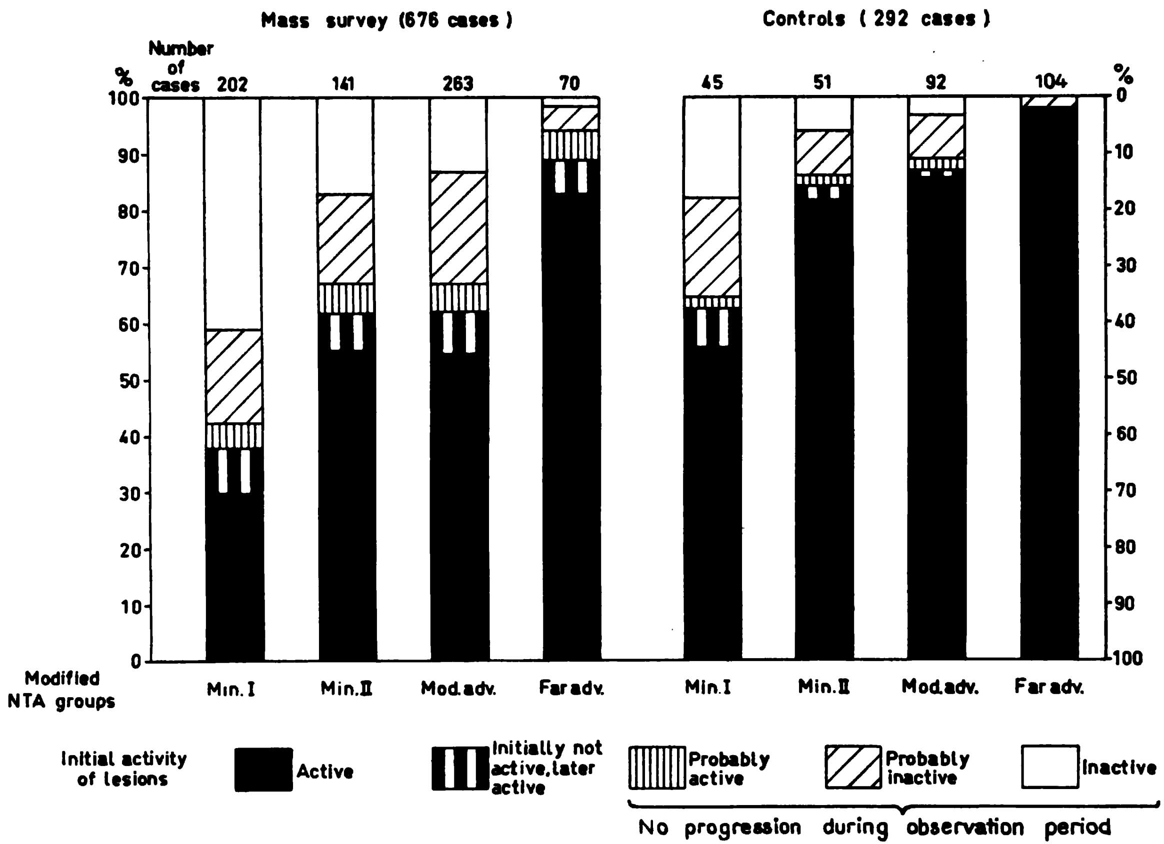


Fig 5. Activity of lesions (in % of cases distributed according to modified NTA classification).

4. *Age and sex*

The 676 cases of mass-survey detected tuberculosis comprised 352 men and 324 women. The 292 cases of the control series consisted of 147 men and 145 women. The sex distribution of the *initially active* cases was also strikingly equal — 171 men and 168 women in the mass survey group and 126 men and 122 women in the controls.

Figure 6 presents the clinical material according to sex and age distribution in 5-year groups. In the mass survey series one sees a shift to higher ages as compared with the controls; about 40 per cent of the former cases and about 26 per cent of the latter were older than 50 years. Common to these higher age groups in both series, however, was a preponderance of men. In the controls the 20 to 24 age group was the largest among the males, whereas in the females the 3 age groups between 15 and 29 years were of equal size. These dominant age groups tallied well with the age morbidity curve for pulmonary tuberculosis in the country as a whole at the time.

For the subsequent analysis of the clinical material, the 5-year age groups were combined into the 6 groups shown in table 6. The age limits for the 6 groups were selected after preliminary studies of the material as regards tuberculosis frequency in relation to age, so that pronounced differences in this respect would not be levelled out by the other cases in the group. Consequently, the age coverage of the various groups differs, and also their numerical basis in the general population.

The 15 to 24 age group is seen in table 6 to comprise 26.4 per cent of all the control cases but only 8.6 per cent of the total mass survey series. Also of the *initially active* controls remarkably many were in this age group — *27* per cent of the men and *32* per cent of the women. Among the initially active mass survey cases aged 15 to 24 years there were approximately twice as many females as males.

The 50 to 69 age group contained more men than women in the total mass survey series and in the total controls. This male preponderance was likewise evident as regards the initially active cases in both series.

5. *Correlation of initial activity to age and sex*

In table 6 and in figures 7 and 8 the cases are grouped according to initial activity of the lesions as well as to age and sex. The profound difference between the mass survey series and the controls as regards initial activity is well apparent. Most of the controls had active tuberculosis. As already mentioned, however, this was a natural consequence of the cir-

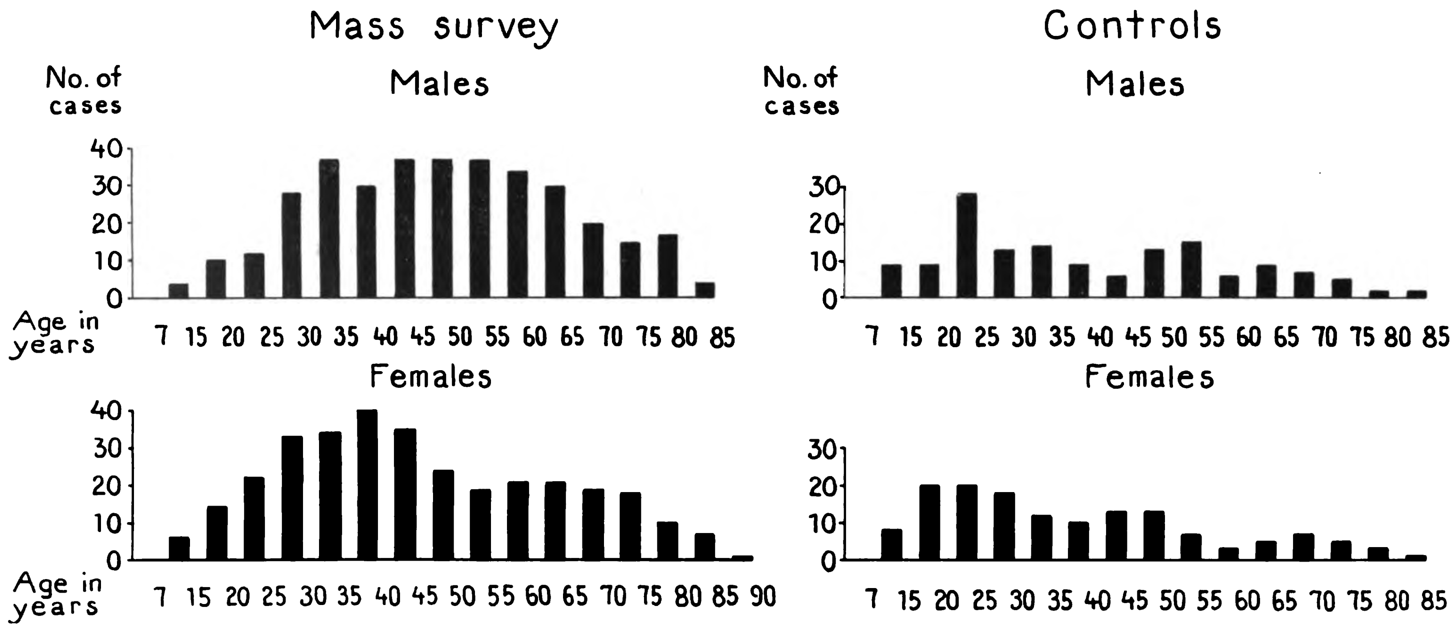


Fig. 6. **Age and sex distribution of all notified cases of pulmonary tuberculosis.**

cumstance that in most of the controls symptoms led to the diagnosis (table 17). Only half of the mass survey cases were initially active. This also was attributable to the mode of diagnosis, viz., without regard to possible symptoms.

6. *Discussion*

The *sex* distribution in the initially active cases was strikingly equal in the mass survey series and in the controls. It is possible to perceive a connection between this finding and the 1946 figures for first hospitalizations for intrathoracic tuberculosis in Sweden. Males and females were equally represented in that year, whereas both before and after 1946 males predominated.

The *age* groups into which the cases were distributed were so constituted that marked differences in frequency of pulmonary tuberculosis between certain ages would not be masked by the other cases in the respective groups. The high frequency of active tuberculosis in young persons was apparent from the fact that about 30 per cent of the active control cases were between 15 and 24 years old. Because tuberculosis in such young persons often produces alarming symptoms, these cases are mainly diagnosed in routine dispensary work and only to a relatively small extent by mass radiography: In the present investigation scarcely 15 per cent of the initially active mass survey cases were aged between 15 and 24 years.

Many writers have pointed out the value of community-wide radiographic surveys for detecting *tuberculosis in the higher age groups*. Mainly from the epidemiologic aspect, *Mascher* (1949), in the original account of the mass survey cases in the present investigation, stressed the importance of diagnosing the numerous cases of tuberculosis in elderly persons. As a rule such persons are less liable to be covered by health control than are younger persons, who may be examined for tuberculosis at schools, workplaces, etc. If one sets the lower age limit at 50 years, 273 cases of tuberculosis were registered as the result of the Södermanland mass survey. With 70 years as the lower limit, 72 cases were registered. However, if only the initially active cases are taken into account, these figures fall to 86 and 13, i. e., 12.7 and 1.9 per cent of all registered mass survey cases.

In figure 9 the various age groups in the mass survey series — total cases and initially active cases — are shown in relation to the corresponding age groups in the general population of Södermanland County. The numerical difference between the active cases and the total cases increased with rising age. In the males, instead of the peak formed by the totals in the two highest age groups, the important, active cases displayed fairly

Table 6. *Initial Activity of Lesions in Various Age Groups*

Age in years	Initial activity of lesions																								Males plus females	
	Active		Initially not active, later active		Probably active (no progression during observation period)		Probably inactive (no progression during observation period)		Inactive (no progression during observation period)		Total		Active		Initially not active, later active		Probably active (no progression during observation period)		Probably inactive (no progression during observation period)		Inactive (no progression during observation period)		Total			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	Mass survey (males)												*Mass survey (females)*													
7—14	4	2.3									4	1.1	5	3.0					1	1.9			6	1.8	10	1.5
15—24	16	9.4					3	5.1	3	4.2	22	6.3	33	19.6	1	6.2			1	1.9	1	1.4	36	11.1	58	8.6
25—34	37	21.6	8	24.2	1	5.6	5	8.5	14	19.7	65	18.5	55	32.7	3	18.8	1	5.9	3	5.8	5	7.0	67	20.7	132	19.5
35—49	57	33.3	14	42.4	7	38.9	9	15.2	17	23.9	104	29.5	46	27.4	6	37.5	3	17.6	15	28.9	29	40.8	99	30.6	203	30.0
50—69	51	29.8	9	27.3	6	33.3	24	40.7	31	43.7	121	34.4	22	13.1	4	25.0	5	29.4	20	38.4	29	40.8	80	24.7	201	29.7
⩾ 70	6	3.6	2	6.1	4	22.2	18	30.5	6	8.5	36	10.2	7	4.2	2	12.5	8	47.1	12	23.1	7	9.9	36	11.1	72	10.7
Total	171	(48.6)	33	(9.4)	18	(5.1)	59	(16.7)	71	(20.2)	352		168	(51.9)	16	(4.9)	17	(5.2)	52	(16.1)	71	(21.9)	324		676	
	Controls (males)												*Controls (females)*													
7—14	9	7.1									9	6.1	8	6.6									8	5.5	17	5.8
15—24	34	27.0					3	23.1			37	25.2	39	32.0							1	11.1	40	27.6	77	26.4
25—34	26	20.6							1	20.0	27	18.4	25	20.5	1	25.0			3	37.5	1	11.1	30	20.7	57	19.5
35—49	25	19.8					2	15.4	1	20.0	28	19.0	28	22.9	1	25.0	1	50.0	1	12.5	5	55.5	36	24.8	64	21.9
50—69	26	20.6	1	100	2	100	6	46.2	2	40.0	37	25.2	15	12.3	2	50.0	1	50.0	2	25.0	2	22.2	22	15.2	59	20.2
⩾ 70	6	4.8					2	15.4	1	20.0	9	6.1	7	5.7					2	25.0			9	6.2	18	6.2
Total	126	(85.7)	1	(0.7)	2	(1.4)	13	(8.8)	5	(3.4)	147		122	(84.1)	4	(2.8)	2	(1.4)	8	(5.5)	9	(6.2)	145		292	

The figures in brackets denote % of the total for the sex within the respective groups.

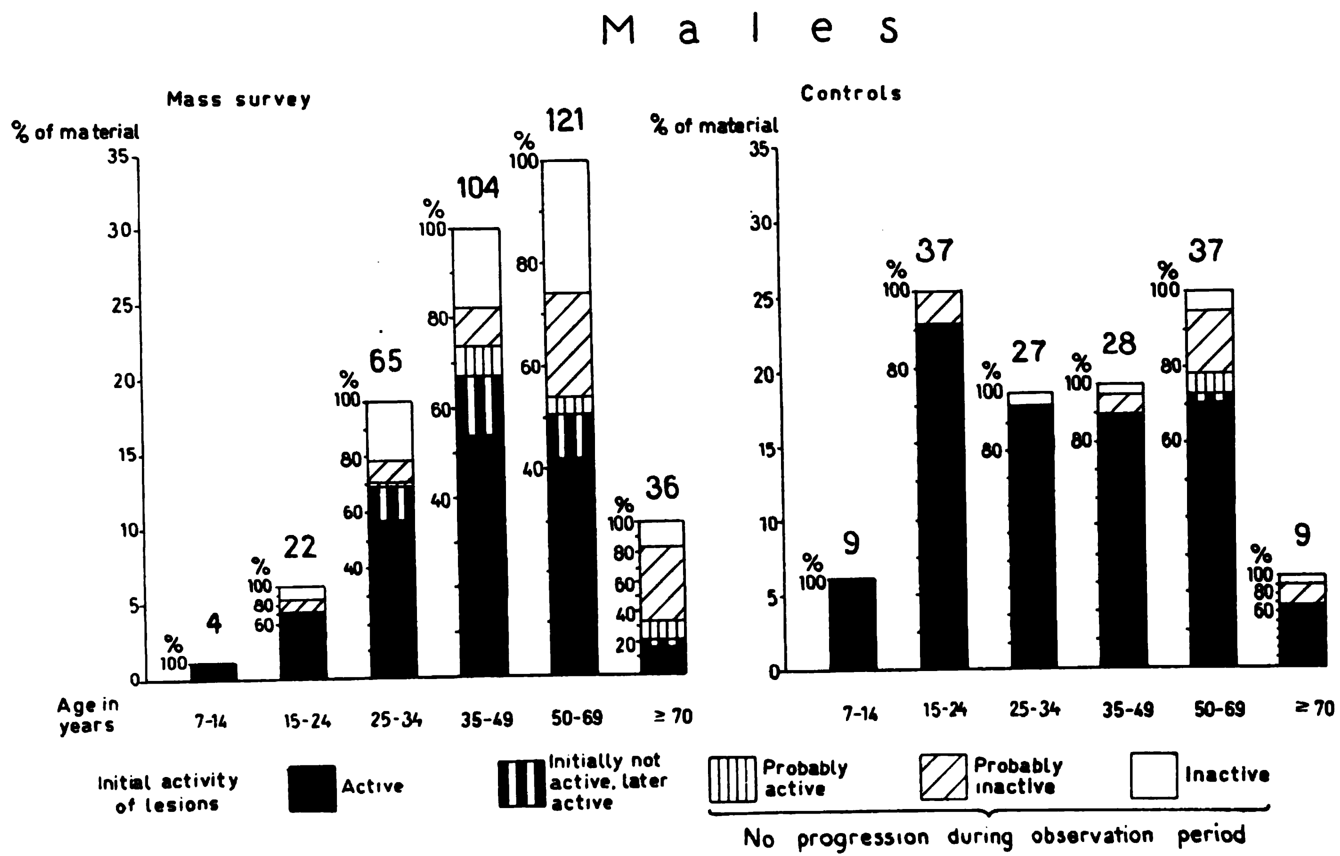


Fig 7. **Initial activity of lesions in various age groups.**

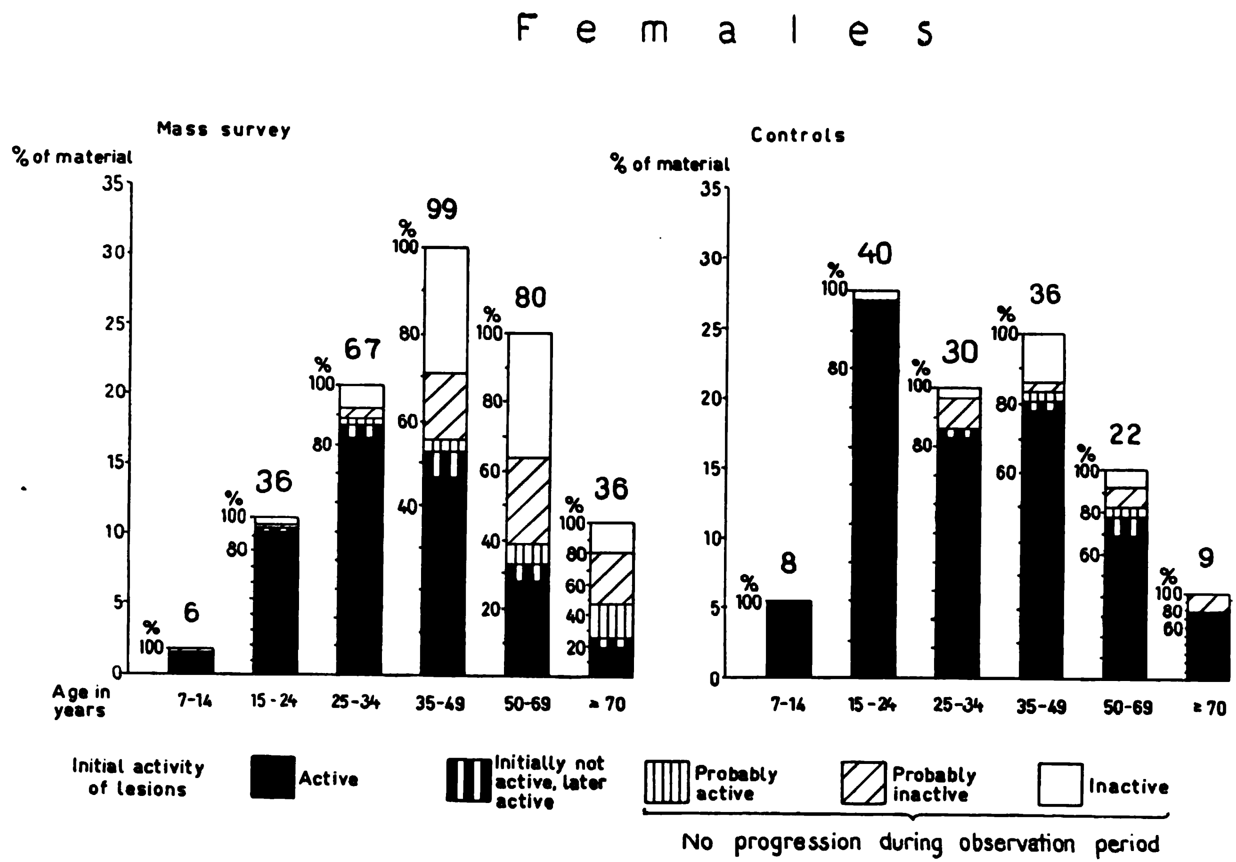


Fig. 8. Initial activity of lesions in various age groups.

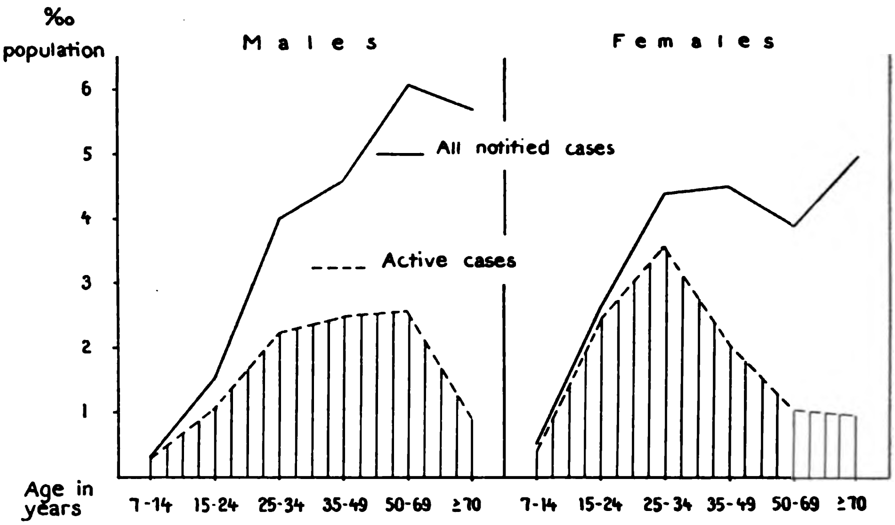


Fig. 9. Pulmonary tuberculosis notified following mass survey in ‰ of age groups in population.

even distribution between 25 and 69 years. In the females the graph of the total groups was fairly evenly maintained from 25 years and upwards, but the active cases showed a pronounced peak at 25 to 34 years.

These observations do not, of course, imply that the cases retrospectively judged not to have had active tuberculosis at the time of mass survey examination did not require supervision, since one cannot always confidently assess activity when making the diagnosis. Moreover, even the retrospective evaluation did not permit classification of all the cases as definitely active or definitely inactive at diagnosis, and some cases without activity at diagnosis became active later. What the observations do show, however, is that primary figures for post-survey notifications of tuberculosis may be misleading if taken as a measure of the distribution of active tuberculosis in various age groups of the general population.

An acceptable *roentgenologic classification* of pulmonary tuberculosis is that of the National Tuberculosis Association of America (NTA), which is based chiefly on the *extent* of the lesions, but is incomplete as regards their *nature*. Among the writers who have remarked on this circumstance were *Fellows, Evans & Stephens* (1949), who further divided their cases into active and inactive. Their object was to obtain a schematic classifying basis for insurance purposes. Although I have not precisely enunciated all roentgenographic manifestations denoting presence or absence

of activity, the nature of the lesions was a highly important consideration in my evaluations in this respect, which were based on long clinical experience.

To judge from the varying frequencies of minimal tuberculosis in community-wide radiographic surveys reported in the literature, "minimal" has received divergent interpretations. Thus, *Rubenstein* (1956) found, in an Australian investigation, that 24 per cent of 696 newly detected cases of active tuberculosis had minimal lesions, whereas the figure reported by *Woodruff* (1956) from a similar investigation in the same country was 43.5 per cent. Of the tuberculosis cases in *Brauner's* (1955) report of mass radiography in California, U. S. A., 26 to 31 per cent were stated to have minimal lesions, and of those from New York State described by *Siegel, Plunkett & Locke* (1955), 51.5 per cent were in the same category. The investigation by *Ames & Schuck* (1953) has already been mentioned; they classed 85.8 per cent of the tuberculosis found in white persons as minimal, including 26.8 per cent with active disease.

Of the mass-survey detected cases of tuberculosis in my investigation, 50.8 per cent of all those notified had minimal lesions according to the NTA definition, and 40.7 per cent of the active cases were in this category. The division of the cases into 20 subgroups in table 5 illustrates the great variation that is possible within each of the three NTA groups and permits a detailed survey of the composition of my clinical material. Although it would have been interesting to retain this subgrouping, several of the subgroups would have been too small for the statistical treatment. The usual NTA classification is therefore mainly used in the continuation of the study, but minimal lesions as a rule are classified into two groups. As well as facilitating investigation of the clinical material, the use of the NTA classification is advantageous for comparisons with the findings of other writers.

CHAPTER VI

COMPARATIVE ANALYSIS CONTINUED ACCORDING TO INITIAL ACTIVITY OF TUBERCULOSIS

Further comparison between the cases of tuberculosis registered as the direct result of the mass survey and the control cases would have been unsatisfactory without the use of an objective factor common to both series. For this purpose I considered the activity of the lesions to be most suitable. *Comparison between the initially active cases* in the mass survey series and in the controls seemed therefore to be the procedure of choice. The strict criteria for classification as active tuberculosis clearly distinguished such cases from those with probably active, probably inactive or inactive disease, which throughout the period of observation showed no definite manifestations of activity. In the continued presentation of the clinical material these cases without definite activity are combined into a single group called "other cases". A third group consists of "initially not active, later active" cases, which displayed aspects of special interest.

1. *Nationality*

In accordance with the statutory requirements in Sweden, a separate register of tuberculosis is kept for persons who are not Swedish citizens. Persons who by birth were foreign subjects but who, by marriage or other means, acquire Swedish citizenship, are eligible for the Swedish register. Consequently, medically similar cases may be entered in different registers. I have not adhered to this system: As far as possible the country of origin has determined the classification of nationality shown in table 7. Non-Swedish persons according to my definition constituted 4.7 per cent of the mass survey series as a whole and 3.4 per cent of the controls; the corresponding frequencies in the initially active cases were 5.6 and 4.0 per cent.

2. *Occupational classification*

In grouping the clinical material according to occupation, the classification used in the Statistical Abstract of Sweden was largely followed, but certain deviations were made for various reasons. As regards distribution of

TABLE 7. *Nationality*

Country of origin	Lesions initially active		Initially not active, later active		Other cases		Total		Lesions initially active		Initially not active, later active		Other cases		Total		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	Mass survey (males)								*Mass survey (females)*									
Sweden	160	93.6	32	97.0	140	94.6	332	94.3	160	95.2	15	93.7	137	97.9	312	96.3	644	95.3
Norway	1	0.6			2	1.4	3	0.8									3	0.4
Finland	1	0.6			3	2.0	4	1.1	1	0.6	1	6.2	1	0.7	3	0.9	7	1.0
Other aliens (non-Scandinavian) .	9	5.3	1	3.0	3	2.0	13	3.9	7	4.2			2	1.4	9	2.8	22	3.3
Total	171		33		148		352		168		16		140		324		676	
	Controls (males)								*Controls (females)*									
Sweden	121	96.0	1	100	20	100	142	96.6	117	95.9	4	100	19	100	140	96.5	282	96.6
Norway									2	1.6					2	1.4	2	0.7
Finland									1	0.8					1	0.7	1	0.3
Other aliens (non-Scandinavian) .	5	4.0					5	3.4	2	1.6					2	1.4	7	2.4
Total	126		1		20		147		122		4		19		145		292	

TABLE 8. *Occupational Status*

Occupational status	Lesions initially active		Initially not active, later active		Other cases		Total		Lesions initially active		Initially not active, later active		Other cases		Total		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	Mass survey (males)								*Mass survey (females)*									
Economically active:																		
Employers	18	10.5	6	18.2	14	9.5	38	10.8	1	0.6					1	0.3	39	5.8
Employees, administrative posts	16	9.4	3	9.1	10	6.8	29	8.2	2	1.2			1	0.7	3	0.9	32	4.7
Other employees	100	58.5	18	54.5	80	54.0	198	56.3	44	26.2	3	18.7	26	18.6	73	22.5	271	40.1
Economically inactive:																		
Housewives									84	50.0	10	62.5	69	49.3	163	50.3	163	24.1
Retired persons (⩾ 67 years) .	10	5.8	3	9.1	34	22.9	47	13.4	9	5.4	2	12.5	35	25.0	46	14.2	93	13.7
School children, students . . .	4	2.3			1	0.7	5	1.4	8	4.8			1	0.7	9	2.8	14	2.1
Physically ill persons	3	1.7			1	0.7	4	1.1									4	0.6
Mentally ill or defective persons	20	11.7	3	9.1	8	5.4	31	8.8	17	10.1	1	6.2	7	5.0	25	7.7	56	8.3
Others									3	1.8			1	0.7	4	1.2	4	0.6
Total	171		33		148		352		168		16		140		324		676	
	Controls (males)								*Controls (females)*									
Economically active:																		
Employers	12	9.5					12	8.2	2	1.6					2	1.4	14	4.8
Employees, administrative posts	4	3.2	1	100			5	3.4	1	0.8	1	25.0	1	5.3	3	2.1	8	2.7
Other employees	85	67.5			13	65.0	98	66.7	45	36.9	2	50.0	3	15.8	50	34.5	148	50.7
Economically inactive:																		
Housewives									46	37.7	1	25.0	12	63.2	59	40.7	59	20.2
Retired persons (⩾ 67 years) .	7	5.5			6	30.0	13	8.8	10	8.2			3	15.8	13	8.9	26	8.9
School children, students . . .	15	11.9			1	5.0	16	10.9	9	7.4					9	6.2	25	8.6
Physically ill persons	1	0.8					1	0.7									1	0.3
Mentally ill or defective persons	2	1.6					2	1.4	3	2.5					3	2.1	5	1.7
Others									6	4.9					6	4.1	6	2.0
Total	126		1		20		147		122		4		19		145		292	

economically active persons as employers, salaried employees or wage earners (the official grouping), the distinction between the last two groups may depend only on such factors as the trade unions to which the persons belong. A preferable classification for present purposes therefore seemed to be that shown in table 8 — employers, administrative employees and other employees.

Among the *economically inactive* persons in table 8 were included, in accordance with accepted international practice, housewives. This group is undoubtedly over-represented both in the mass survey series and in the controls, since married women were not always questioned concerning possible gainful employment. As retired persons were classed those aged 67 years or over, 67 being the commencing age for old age pensions in Sweden. The remaining economically inactive persons were grouped as school children and students, sick persons and "others"; the last category comprised adult daughters working in the home, etc.

Only the initially active cases are shown in table 9. The official classification of occupations is followed here and to it are separately added housewives and "non-working persons". It should be noted, however, that in table 9 retired persons are shown according to their earlier profession, which entails some numerical differences between this table and table 8.

Particularly in the female patients there was, as already indicated, some uncertainty concerning occupational classification. This applied not only to housewives, but also to, for instance, clerkesses, who in some cases had to be classed according to probable branch of industry.

In three of the groups in table 9 there were subdivisions of occupation which invite interest as regards tuberculosis. These were food handling and work with children or sick persons. The mass radiographic survey revealed 16 cases of active tuberculosis in these categories, or 4.7 per cent of the total initially active cases. Among the initially active controls 13, or 5.2 per cent, were in the occupations in question.

The good agreement between the two series as regards occupational distribution is evident from table 9. The differences in table 8, e. g., more children and fewer housewives in the controls than in the mass survey series, mainly reflect the differences in the age composition of the series (table 6).

3. *Familial or environmental tuberculosis*

Since all the patients had tuberculous lesions, whether or not these were active at the time of my study, it should be of interest to compare the total mass survey series with the total controls as regards heredity for tuberculosis. The information available is presented in table 10.

Table 9. *Occupations in Initially Active Cases*

Occupations[1]	Mass survey				Controls			
	Males		Females		Males		Females	
	No.	%	No.	%	No.	%	No.	%
Agriculture, forestry, fishing	35	20.5			21	16.7		
Manufacturing, construction, mining, etc.:								
Food industry	2	1.2	1	0.6	1	0.8	5	4.1
Other industries	76	44.4	16	9.6	69	54.7	19	15.6
Transport and communications	15	8.8	2	1.2	6	4.8	1	0.8
Commerce:								
Food trade			2	1.2	1	0.8		
Other trades	8	4.7	7	4.2	7	5.5	6	4.9
General administration and professions:								
Public health	4	2.4	3	1.8			4	3.3
Education	1	0.6	3	1.8	1	0.8	1	0.8
Other occupations	3	1.8	1	0.6	2	1.6	1	0.8
Domestic service			13	7.7			11	9.0
Housewives			92	54.8			56	45.9
Non-working persons[2]	27	15.7	28	16.7	18	14.3	18	14.8
Total	171		168		126		122	

[1] Retired persons shown according to their previous occupations.
[2] Denotes "economically inactive" persons minus housewives and retired persons (see table 8).

The most important categories in this respect would seem to be parents and siblings. Of the mass survey series 22.1 per cent reported that some form of tuberculosis was or had been present in one or more of such relatives, and in the control cases this figure was 31.8 per cent.

It was expected that there would be more histories of tuberculosis in relatives or other contacts in the control cases than in the mass survey series, as more than 10 per cent of the controls were diagnosed following examination of contacts (table 17). Tuberculosis discovered by examination of contacts of the mass survey cases, on the other hand, could not, according to the conditions of the study, be included in the survey series.

4. *Previous manifestations of tuberculosis*

In the patients listed as having previous manifestations of tuberculosis, there was a varying interval between recognition of these lesions and the

TABLE 10. *Familial or Environmental Tuberculosis*

Tuberculous relatives or environment	Lesions initially active		Initially not active, later active		Other cases		Total		Lesions initially active		Initially not active, later active		Other cases		Total		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	Mass survey (males)								*Mass survey (females)*									
None known	90	52.6	16	48.5	95	64.2	201	57.1	85	50.6	7	43.8	81	57.9	173	53.4	374	55.3
Both parents	2	1.2			1	0.7	3	0.8	2	1.2					2	0.6	5	0.7
One parent plus sibling(s)	7	4.1	3	9.1	2	1.4	12	3.4	7	4.2			7	5.0	14	4.3	26	3.9
One parent	12	7.0	1	3.0	11	7.4	24	6.8	17	10.1			6	4.3	23	7.1	47	7.0
Sibling(s)	24	14.0	4	12.1	10	6.8	38	10.8	22	13.1	3	18.7	8	5.7	33	10.2	71	10.5
Spouse and/or child(ren)	5	2.9	1	3.0	2	1.4	8	2.3	2	1.2	1	6.2	8	5.7	11	3.4	19	2.8
Other relatives	6	3.6	1	3.0	4	2.7	11	3.1	13	7.7	3	18.7	5	3.6	21	6.5	32	4.7
Contact with tuberculous nonrelatives	2	1.2			2	1.4	4	1.1	5	3.0			1	0.7	6	1.8	10	1.5
No information	23	13.4	7	21.2	21	14.2	51	14.5	15	8.9	2	12.5	24	17.1	41	12.7	92	13.6
Total	171		33		148		352		168		16		140		324		676	
	Controls (males)								*Controls (females)*									
None known	64	50.8	1	100	7	35.0	72	49.0	45	36.9	2	50.0	6	31.6	53	36.6	125	42.8
Both parents	2	1.6					2	1.4	2	1.6	1	25.0			3	2.1	5	1.7
One parent plus sibling(s)	4	3.2					4	2.7	5	4.1			3	15.8	8	5.5	12	4.1
One parent	10	7.9			1	5.0	11	7.5	14	11.5	1	25.0			15	10.3	26	8.9
Sibling(s)	20	15.9			2	10.0	22	15.0	26	21.3			2	10.5	28	19.3	50	17.1
Spouse and/or child(ren)	3	2.4			3	15.0	6	4.1	7	5.7			2	10.5	9	6.2	15	5.2
Other relatives	7	5.5			1	5.0	8	5.4	8	6.6					8	5.5	16	5.5
Contact with tuberculous nonrelatives	7	5.5					7	4.8	8	6.6					8	5.5	15	5.2
No information	9	7.1			6	30.0	15	10.2	7	5.7			6	31.6	13	8.9	28	9.6
Total	126		1		20		147		122		4		19		145		292	

TABLE 11. *Previous Intrathoracic Tuberculous Manifestations*

Relevant history	Lesions initially active		Initially not active, later active		Other cases		Total		Lesions initially active		Initially not active, later active		Other cases		Total		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	Mass survey (males)								*Mass survey (females)*									
No intrathoracic tuberculosis . . .	130	76.0	23	69.7	108	73.0	261	74.2	134	79.8	11	68.8	101	72.2	246	76.2	507	75.0
Pleurisy	17	9.9	3	9.1	11	7.4	31	8.8	11	6.5			9	6.4	20	6.1	51	7.5
Hilar adenitis					2	1.4	2	0.6	3	1.8	1	6.2			4	1.2	6	0.9
Primary pulmonary tuberculosis .					1	0.7	1	0.3									1	0.1
Sputum-neg., postprimary ditto . .	1	0.6			6	4.0	7	2.0	5	3.0	1	6.2	6	4.3	12	3.6	19	2.8
Sputum-pos., » » . .	4	2.3	2	6.1	1	0.7	7	2.0	3	1.8	1	6.2	3	2.1	7	2.2	14	2.1
Not known	19	11.1	5	15.1	19	12.8	43	12.2	12	7.1	2	12.5	21	15.0	35	10.8	78	11.6
Total	171		33		148		352		168		16		140		324		676	
	Controls (males)								*Controls (females)*									
No intrathoracic tuberculosis . . .	85	67.5	1	100	14	70.0	100	68.0	94	77.1	4	100	8	42.1	106	73.1	206	70.5
Pleurisy	17	13.5			1	5.0	18	12.2	14	11.5			4	21.0	18	12.4	36	12.3
Hilar adenitis	7	5.5					7	4.8	2	1.6					2	1.4	9	3.1
Sputum-neg., postprimary pulmonary tuberculosis	7	5.5			1	5.0	8	5.4	6	4.9			2	10.6	8	5.5	16	5.5
Sputum-pos. ditto	4	3.2			1	5.0	5	3.4					1	5.3	1	0.7	6	2.0
Not known	6	4.8			3	15.0	9	6.1	6	4.9			4	21.0	10	6.9	19	6.5
Total	126		1		20		147		122		4		19		145		292	

Table 12. *Previous Extrathoracic Tuberculous Manifestations*

Relevant history	Lesions initially active		Initially not active, later active		Other cases		Total		Lesions initially active		Initially not active, later active		Other cases		Total		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	Mass survey (males)								*Mass survey (females)*									
No extrathoracic tuberculosis	147	86.0	26	78.8	126	85.1	299	84.9	141	83.9	13	81.2	107	76.4	261	80.6	560	82.9
Erythema nodosum	3	1.7	2	6.1	1	0.7	6	1.7	11	6.6			9	6.4	20	6.1	26	3.9
Cervical adenitis					1	0.7	1	0.3	3	1.8	1	6.2	2	1.4	6	1.8	7	1.0
Mesenteric adenitis					1	0.7	1	0.3	1	0.6					1	0.3	2	0.3
Genito-urinary tuberculosis	1	0.6					1	0.3									1	0.1
Skeletal tuberculosis	1	0.6					1	0.3									1	0.1
Not known	19	11.1	5	15.1	19	12.8	43	12.2	12	7.1	2	12.5	22	15.7	36	11.1	79	11.7
Total	171		33		148		352		168		16		140		324		676	
	Controls (males)								*Controls (females)*									
No extrathoracic tuberculosis	114	90.5	1	100	16	80.0	131	89.1	95	77.9	4	100	12	63.2	111	76.5	242	82.9
Erythema nodosum or phlyctenular conjunctivitis	2	1.6					2	1.4	15	12.3			1	5.3	16	11.0	18	6.2
Cervical adenitis	2	1.6			1	5.0	3	2.0	2	1.6			1	5.3	3	2.1	6	2.0
Mesenteric adenitis									2	1.6					2	1.4	2	0.7
Genito-urinary tuberculosis	1	0.8					1	0.7	2	1.6					2	1.4	3	1.0
Skeletal tuberculosis	1	0.8					1	0.7					1	5.3	1	0.7	2	0.7
Not known	6	4.8			3	15.0	9	6.1	6	4.9			4	21.0	10	6.9	19	6.5
Total	126		1		20		147		122		4		19		145		292	

diagnosis of pulmonary disease which led to inclusion in the present study. Those with previous pulmonary tuberculosis, however, had been considered cured and had been freed from supervision.

The patients with a verified history of *intrathoracic tuberculosis* are shown in table 11. As 11.3 per cent of the controls were found to have pulmonary lesions in connection with observation for other (previous or current) tuberculous manifestations (table 17), it was not surprising that previous tuberculosis was more common among this series than among the mass survey cases. Thus, 12.3 per cent of the total controls had a history of pleurisy, but only 7.5 per cent of the total mass survey series, and the respective frequencies of hilar adenitis were 3.1 and 0.9 per cent. Similarly, it is to be expected that a person who has already experienced pulmonary tuberculosis will seek medical advice for relatively insignificant symptoms, even though his name has been deleted from the tuberculosis register. The frequencies of postprimary pulmonary tuberculosis in the anamnesis thus were 7.5 per cent in the control cases and 4.9 per cent in the mass survey series.

Extrathoracic tuberculosis which preceded the present episode of pulmonary tuberculosis is shown in table 12. For the reasons stated concerning intrathoracic disease, earlier extrathoracic tuberculosis was also more common in the controls than in the mass survey cases. The preponderance of females in both series was largely ascribable to the higher frequency of erythema nodosum in them than in the males.

In the initially active cases the tendencies as regards tuberculosis in the anamnesis were similar to those in the respective complete series.

5. *Initial bacteriologic findings*

The bacteriologic studies made in association with diagnosis of tuberculosis in the present study comprised routine procedures and are presented in table 13. In the few cases in which other tests were used, these were classed with the most closely comparable procedures. When several tests were made in the same case, that providing the strongest evidence of positive or negative results was selected. For instance, when direct microscopy of a sputum smear and guinea pig test of gastric washings both showed tubercle bacilli, the former test was included in table 13, and negative gastric washings were accounted more importance than negative direct microscopy of sputum.

Of the total mass survey cases 85.7 per cent and of the total control cases 93.5 per cent were bacteriologically examined in association with diagnosis. Positive findings were recorded in 22.9 per cent of the former

ABLE 13. *Initial Bacteriologic Findings*

itial tests for ibercle bacilli	Lesions initially active			Initially not active, later active		Other cases		Total			Lesions initially active			Initially not active, later active		Other cases		Total			Males plus females		
	No.	%		No.	%	No.	%	No.	%		No.	%		No.	%	No.	%	No.	%		No.	%	
	Mass survey (males)										*Mass survey (females)*												
ositive:																							
Sputum, direct smear .	43	25.1	48.5					43	12.2	23.6	27	16.1	42.9					27	8.3	22.2	70	10.4	22.9
Sputum, culture	1	0.6						1	0.3												1	0.1	
Gastric washings[1] . . .	39	22.8						39	11.1		45	26.8						45	13.9		84	12.4	
egative:																							
Sputum, direct smear .	19	11.1	44.4	6	18.2	44	29.7	69	19.6	62.8	12	7.1	48.8	4	25.0	40	28.6	56	17.3	62.6	125	18.5	62.7
Sputum, culture . . .						1	0.7	1	0.3		1	0.6				2	1.4	3	0.9		4	0.6	
Gastric washings[1] . . .	57	33.3		21	63.6	73	49.3	151	42.9		69	41.1		9	56.2	66	47.1	144	44.4		295	43.6	
o test initially	12	7.0		6	18.2	30	20.3	48	13.6		14	8.3		3	18.7	32	22.9	49	15.1		97	14.3	
Total	171			33		148		352			168			16		140		324			676		
	Controls (males)										*Controls (females)*												
ositive:																							
Sputum, direct smear .	73	57.9	69.0					73	49.7	59.2	61	50.0	54.9					61	42.1	46.2	134	45.9	52.7
Gastric washings[1] . . .	14	11.1						14	9.5		6	4.9						6	4.1		20	6.8	
egative:																							
Sputum, direct smear .	12	9.5	25.4			7	35.0	19	12.9	33.3	9	7.4	39.4	1	25.0	4	21.0	14	9.7	48.3	33	11.3	40.7
Sputum, culture																1	5.3	1	0.7		1	0.3	
Gastric washings[1] . . .	20	15.9		1	100	9	45.0	30	20.4		39	32.0		3	75.0	13	68.4	55	37.9		85	29.1	
o test initially	7	5.5				4	20.0	11	7.5		7	5.7				1	5.3	8	5.5		19	6.5	
Total	126			1		20		147			122			4		19		145			292		

culture and/or guinea-pig test

Table 14. *Initial Erythrocyte Sedimentation Rate*

E. S. R. (mm/1 hour)		Lesions initially active		Initially not active, later active		Other cases		Total		Lesions initially active		Initially not active, later active		Other cases		Total		Males plus females	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
		Mass survey (males)								*Mass survey (females)*									
Males	*Females*																		
< 6	<10	52	30.4	14	42.4	47	31.8	113	32.1	46	27.3	5	31.2	43	30.7	94	29.0	207	30.6
6—10	10—15	50	29.2	8	24.2	29	19.6	87	24.7	38	22.6	4	25.0	26	18.6	68	21.0	155	22.9
11—20	16—20	26	15.2	5	15.1	33	22.3	64	18.2	23	13.7	5	31.2	14	10.0	42	13.0	106	15.7
Males and females																			
21—30		14	8.2	1	3.0	9	6.1	24	6.8	25	14.9			21	15.0	46	14.2	70	10.4
31—40		7	4.1			4	2.7	11	3.2	9	5.4			3	2.1	12	3.7	23	3.4
41—60		9	5.3			2	1.3	11	3.2	12	7.1	2	12.5	5	3.6	19	6.9	30	4.4
> 60		4	2.3	1	3.0	1	0.7	6	1.7	8	4.8			3	2.1	11	3.4	17	2.5
Not measured		9	5.3	4	12.1	23	15.5	36	10.2	7	4.2			25	17.9	32	9.9	68	10.1
	Total	171		33		148		352		168		16		140		324		676	
		Controls (males)								*Controls (females)*									
Males	*Females*																		
< 6	<10	19	15.1	1	100	8	40.0	28	19.0	14	11.5	1	25.0	7	36.8	22	15.2	50	17.1
6—10	10—15	19	15.1			1	5.0	20	13.6	15	12.3	1	25.0	1	5.3	17	11.7	37	12.6
11—20	16—20	20	15.9			4	20.0	24	16.3	11	9.0			3	15.8	14	9.6	38	13.0
Males and females																			
21—30		14	11.1			3	15.0	17	11.6	15	12.3			3	15.8	18	12.4	35	12.0
31—40		12	9.5			2	10.0	14	9.5	15	12.3	1	25.0	2	10.5	18	12.4	32	11.0
41—60		13	10.3					13	8.8	20	16.4			2	10.5	22	15.2	35	12.0
> 60		24	19.0			2	10.0	26	17.7	27	22.1			1	5.3	28	19.3	54	18.5
Not measured		5	4.0					5	3.4	5	4.1	1	25.0			6	4.1	11	3.8
	Total	126		1		20		147		122		4		19		145		292	

series and in 52.7 per cent of the latter. The corresponding figures for the initially active cases were 45.7 and 62.1 per cent. Of the cases with negative bacteriologic findings, 69.6 per cent of those discovered by mass survey and 71.4 per cent of the control series were studied by culture and/or guinea pig tests of gastric washings. The great differences as regards the proportion of cases in which direct microscopy of sputum revealed tubercle bacilli are also seen in table 13. In the total controls this frequency was 45.9 per cent and in the total survey series it was 10.4 per cent; in the initially active cases the respective figures were 54.0 and 20.6 per cent. These differences were, of course, a reflection of the greater number of advanced cases of tuberculosis among the controls than in the mass survey group.

Only relatively few cases were not bacteriologically examined in connection with the diagnosis, and the clinical material may be regarded as well investigated from this aspect, both quantitatively and qualitatively.

6. *Initial erythrocyte sedimentation rate*

In estimating E.S.R. values (Westergren), the limits for the low categories were set higher for women than for men. Table 14 shows the E.S.R. readings at the time of diagnosis. As normal values were chosen less than 6 mm/l hour in males and less than 10 mm in females. Readings between 6 and 10 mm in males and between 10 and 15 mm in females were considered to be borderline values. Higher readings were classed as elevated.

Elevated E.S.R. was somewhat more common in the female patients than in the males, viz., in 41.2 *v.* 33.0 per cent of the total survey series and in 68.9 *v.* 64.0 per cent of the controls. In the initially active cases this difference was a little more pronounced; in the mass survey series 45.9 per cent of the females and 35.1 per cent of the males had elevated E.S.R., and in the controls these frequencies were 72.1 and 65.8 per cent. In all, 36.4 per cent of the mass survey cases and 66.4 per cent of the control cases had elevated E.S.R. at diagnosis. These differences were yet another expression of the greater frequency of advanced disease in the controls.

7. *Current tuberculous complications*

In table 15 are reported the other manifestations of tuberculosis which were discovered simultaneously with the pulmonary lesions pertinent to the present study. Both the number of complications and the total of the affected persons were greater in the control material than in the mass survey

TABLE 15. *Tuberculous Complications*

Complications	Lesions initially active		Initially not active, later active		Other cases		Total		Lesions initially active		Initially not active, later active		Other cases		Total		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	Mass survey (males)								*Mass survey (females)*									
No tuberculous complications	164	95.9	33	100	148	100	345	98.0	158	94.0	16	100	140	100	314	96.9	659	97.5
Bronchial tuberculosis	7	4.1					7	2.0	4	2.4					4	1.2	11	1.6
Intestinal ,,									1	0.6					1	0.3	1	0.1
Laryngeal ,, plus intestinal ,,									1	0.6					1	0.3	1	0.1
Pleural ,,									4	2.4					4	1.2	4	0.6
Total	171		33		148		352		168		16		140		324		676	
	Controls (males)								*Controls (females)*									
No tuberculous complications	95	75.4	1	100	19	95.0	115	78.2	85	69.7	4	100	19	100	108	74.5	223	76.4
Bronchial tuberculosis	9	7.1					9	6.1	6	4.9					6	4.1	15	5.1
Laryngeal ,,	4	3.2					4	2.7	4	3.3					4	2.8	8	2.7
Intestinal ,,	3	2.4					3	2.0	9	7.4					9	6.2	12	4.1
Laryngeal ,, plus intestinal ,,	1	0.8					1	0.7									1	0.3
Pleural ,,	10	7.9					10	6.8	11	9.0					11	7.6	21	7.2
Skeletal ,,	3	2.4					3	2.0	2	1.6					2	1.4	5	1.7
Miliary ,,	1	0.8					1	0.7	2	1.6					2	1.4	3	1.0
Tuberculous cervical adenitis					1	5.0	1	0.7									1	0.3
Erythema nodosum									3	2.5					3	2.1	3	1.0
Total	126		1		20		147		122		4		19		145		292	

series. Also for each single complication there was a preponderance of control cases. All the extrapulmonary tuberculosis, except in a case with hilar adenitis, occurred in persons with active pulmonary lesions.

Pleurisy was present at diagnosis of pulmonary tuberculosis in 8.5 per cent of the active controls, but in only 1.2 per cent of the active mass survey cases, and the respective frequencies of bronchial tuberculosis (in almost all cases bronchoscopically proven) were 6.0 and 3.2 per cent. Laryngeal and intestinal tuberculosis should be considered separately as, at the time in question, they most commonly arose from terminal spread of tuberculosis. The larynx or the intestine, or both, showed tuberculosis in 8.5 per cent of the active control cases as compared with 0.6 per cent of the active mass survey series. These conditions were found only when the pulmonary lesions were moderately or far advanced, in contrast to bronchial tuberculosis and pleurisy, which could occur in all stages of pulmonary disease. Intestinal tuberculosis was in all cases verified by autopsy examination.

8. *Nontuberculous complications*

The nontuberculous conditions which may be of interest when they complicate pulmonary tuberculosis, and which were present in my clinical material, are shown in table 16. Such complications were relatively rare, except for mental illness or deficiency, which were more common in the mass survey series than in the control cases. This probably was inevitable, as mentally abnormal persons cannot understand and communicate symptoms to the same extent as can mentally healthy persons. It follows that the need for mass radiography is increased in patients with mental illness or deficiency. This group is separately presented in chapter X.

9. *Discussion*

Anderson, Enterline, Hill & Roberts (1954), in the investigation earlier reviewed in this study, reflected on the hypothesis that an ideal control group for mass-survey detected tuberculosis could be obtained if one neglected to inform randomly selected persons of positive findings at mass radiography, but allowed them to carry on as usual until the disease possibly was rediscovered by other means. Such an experiment is, of course, unacceptable. These writers therefore expressed the opinion that the most practical method of obtaining controls is that used in their study — and later also in mine — viz., to collect a group of persons with active pulmo-

TABLE 16. *Nontuberculous Complications*

Complications	Lesions initially active		Initially not active, later active		Other cases		Total		Lesions initially active		Initially not active, later active		Other cases		Total		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	Mass survey (males)								*Mass survey (females)*									
No nontuberculous complications	143	83.6	28	84.8	134	90.5	305	86.6	134	79.8	14	87.5	127	90.7	275	84.9	580	85.8
Mental deficiency	4	2.3					4	1.4	6	3.6			2	1.4	8	2.5	12	1.8
Mental illness	16	9.4	3	9.1	8	5.4	27	7.7	11	6.5	1	6.2	5	3.6	17	5.2	44	6.5
Diabetes mellitus	3	1.7					3	0.8	4	2.4			1	0.7	5	1.5	8	1.2
Polyarthritis	3	1.7	1	3.0	1	0.7	5	1.4	1	0.6	1	6.2	2	1.4	4	1.2	9	1.3
Gastric resection	1	0.6					1	0.3	1	0.6					1	0.3	2	0.3
Pregnancy and/or lactation period									9	5.4					9	2.8	9	1.3
Asthma, emphysema, etc. . . .	1	0.6	1	3.0	5	3.4	7	2.0	2	1.2			3	2.1	5	1.5	12	1.8
Total	171		33		148		352		168		16		140		324		676	
	Controls (males)								*Controls (females)*									
No nontuberculous complications	117	92.9	1	100	17	85.0	135	91.8	105	86.1	3	75.0	18	94.7	126	86.9	261	89.4
Mental deficiency									4	3.3					4	2.8	4	1.4
Mental illness	2	1.6					2	1.4	2	1.6					2	1.4	4	1.4
Diabetes mellitus	2	1.6					2	1.4	4	3.3					4	2.8	6	2.0
Polyarthritis	2	1.6					2	1.4	1	0.8					1	0.7	3	1.0
Gastric resection	1	0.8					1	0.7	1	0.8					1	0.7	2	0.7
Lactation period									5	4.1					5	3.4	5	1.7
Asthma, emphysema, etc. . . .	2	1.6			3	15.0	5	3.4			1	25.0	1	5.3	2	1.4	7	2.4
Total	126		1		20		147		122		4		19		145		292	

nary tuberculosis from the same district but by other diagnostic techniques than mass survey.

The comparison between my two series of tuberculous persons thus concerned mainly those with active disease at the time of diagnosis.

In contrast to most American studies of mass radiography, my clinical material consisted exclusively of white persons. Aliens other than Norwegians and Finns comprised only 3.3 per cent of the total mass survey series and 2.4 per cent of all the controls.

The various factors which are discussed in this chapter were intended only to provide as faceted a basis as possible for the comparison between the two series. They were not meant to serve as a basis for comparisons with the experience of other writers concerning the importance of the factors for the prognosis of tuberculosis in general.

The anamnestic data were collected from out-patient and in-patient records and were somewhat more complete in the control series, as these patients were hospitalized rather more than were the mass survey cases (fig. 14). Because gastric lavage could be performed at all the 20 regional tuberculosis dispensaries in Södermanland County, the patients were well examined from the bacteriologic aspect. In the entire observation period 97.9 per cent of the active mass survey cases and 97.6 per cent of the active controls were examined for tubercle bacilli.

The erythrocyte sedimentation rate was extensively studied; among the active cases only 4.1 per cent of the controls and 4.7 per cent of the mass survey cases were not examined in this way at the time of diagnosis. The definition of elevated E.S.R. (more than 10 mm/l hour in males and more than 15 mm in females) tallied with that used by Westergren's co-worker *Berlin* (1957). Temperature and possible shift to the left in the white blood count were not measured in a sufficient number of the mass survey cases to permit comparisons. Nor is definitive information to be expected from these tests in early, relatively asymptomatic but active pulmonary tuberculosis.

The extrapulmonary tuberculous lesions which were found simultaneously with the pulmonary tuberculosis should be regarded as extensions of the pulmonary lesions when they affected the respiratory tract or the digestive canal. In a study spanning the years 1948 to 1950 (*Källqvist* 1951), secondary intestinal tuberculosis was demonstrated at autopsy in 39.4 per cent of cases of fatal phthisis in which antimicrobial medication had not been given. It was natural that intestinal or laryngeal spread should be more common in the series for whose diagnosis symptoms were highly important, i.e., the control series. Extrapulmonary tuberculous manifestations in other sites than the respiratory or digestive systems were numerically relatively insignificant; they were present in 12 (4.1 per cent) of all

the control cases. The nontuberculous complications had approximately the same, low frequency in both series, except as regards mentally ill or deficient persons, who are separately reported in chapter X.

That the frequency of tuberculosis in relatives or nonfamilial contacts was greater in the controls than in the mass survey cases was not surprising, as the routine work of tuberculosis dispensaries includes investigations among the contacts of tuberculous persons. Nor was the somewhat higher incidence of anamnestic tuberculosis in the controls unexpected, since a few patients were already under supervision for nonpulmonary tuberculosis when the pulmonary lesions supervened and, further, a person who has earlier had tuberculosis will readily seek medical advice for mild symptoms, even after he has been declared free from all suspicion of active disease.

In this analysis no decisive differences were found between the mass survey and the control series which could not be attributed to the differing ways in which the cases were diagnosed — on the one hand the rapid inventory of communities by mass radiography, and on the other hand the more constant but less deeply penetrating routine activities of tuberculosis control.

CHAPTER VII

REASONS WHY THE CONTROL CASES SOUGHT MEDICAL ADVICE

While the reason for diagnosis was uniform in the mass survey cases, it varied considerably in the control series. Pulmonary tuberculosis in the control cases was diagnosed because of symptoms from this or other disease, or because of contact with tuberculous persons, or at routine health control examinations. This last reason concerned mainly children and young adults.

1. *Distribution in the initially active cases*

In table 17 the control series is divided into initially active cases and other cases. The second group comprised only 44 persons, and as their reasons for seeking medical advice by and large resembled those in the initially active cases, the following discussion is confined to the active cases. The frequency figures should be regarded as minima, since each patient is represented once only, viz., with the symptom or reason which was the direct cause of his coming to the notice of the tuberculosis dispensary.

a) Symptoms of pulmonary tuberculosis. In 11.7 per cent of the initially active cases cough alone, and in a further 19.8 per cent cough plus pyrexia with or without night-sweats, led the patients to seek medical advice. This symptom group contained more females than males (36.1 *v.* 27.0 per cent). As haemoptysis was classed blood-stained sputum as well as frank coughing up of blood. This was the primary symptom in 12.9 per cent of the active cases and was commoner in males than in females. Haemoptysis, cough, pyrexia and night-sweats, singly or in combinations, caused 52.5 per cent of the female patients and 45.3 per cent of the males to seek advice. Pleuritic pain was regarded as their most important symptom by 8.7 per cent of the males and 6.6 per cent of the females. Excessive tiredness is a common complaint in pulmonary tuberculosis, but by itself seldom causes a patient to request examination. It is readily disclosed when the patient is questioned, but as a rule he ascribes his fatigue to other causes than illness, e. g., to overwork and delays approaching a physician until graver symptoms appear. Tiredness as a dominating symptom was rare in these control cases.

TABLE 17. *Primary Reasons for Seeking Medical Advice (Control Cases)*

Advice primarily sought for	Lesions initially active						Other cases						All cases	
	Males		Females		Males plus females		Males		Females		Males plus females			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Symptoms of pulmonary tuberculosis:														
Haemoptysis	19	15.1	13	10.7	32	12.9	1	4.8	2	8.7	3	6.8	35	12.0
Cough	14	11.1	15	12.3	29	11.7	1	4.8			1	2.3	30	10.3
Cough, pyrexia, with or without night-sweats	20	15.9	29	23.8	49	19.8	5	23.8	6	26.1	11	25.0	60	20.5
Pyrexia with or without night-sweats	4	3.2	7	5.7	11	4.4			1	4.3	1	2.3	12	4.1
Pleurisy-type pain	11	8.7	8	6.6	19	7.7			3	13.0	3	6.8	22	7.5
Tiredness	3	2.4	4	3.3	7	2.8	1	4.8			1	2.3	8	2.7
Other diseases:														
Nonpulmonary tuberculosis	8	6.3	20	16.4	28	11.3	2	9.5	3	13.0	5	11.4	33	11.3
Nontuberculous disease	10	7.9	5	4.1	15	6.0	2	9.5	5	21.7	7	15.9	22	7.5
Fortuitous findings:														
Tuberculosis contacts	11	8.7	16	13.1	27	10.9	2	9.5	2	8.7	4	9.1	31	10.6
Examination for health certificate, national service, etc.	26	20.6	5	4.1	31	12.5	7	33.3	1	4.3	8	18.2	39	13.4
Total	126		122		248		21		23		44		292	

b) **Nonpulmonary tuberculous manifestations.** These were first recognized in some cases before and in others simultaneously with the pulmonary lesions. The most common of such manifestations was erythema nodosum, which was present in 12 of the 28 cases. All 12 were females, which was reflected in the fact that 16.4 per cent of the females with active pulmonary lesions but only 6.3 per cent of the males came to the tuberculosis dispensary's notice because of extrapulmonary tuberculous conditions. The sex distribution in these cases was as follows.

	Females	Males
Erythema nodosum	11	
Exudative pleurisy	4	2
Skeletal tuberculosis	1	3
Phlyctenular conjunctivitis	1	
Hilar adenitis		3
Genito-urinary tuberculosis	1	
Mesenteric adenitis	1	
Cervical adenitis plus erythema nodosum	1	

c) **Nontuberculous disease.** Routine examination in nontuberculous disease led to the detection of pulmonary tuberculosis in 15 cases (6 per cent of all the active group). Cardiac disease was the nontuberculous condition in 8 of these cases, and among the others were 1 with diabetes mellitus and 2 with gastric disorder.

d) **Examination of tuberculosis contacts and routine health control.** The patients who were found to have pulmonary tuberculosis following examination as contacts of tuberculous persons comprised 10.9 per cent of all the active control cases and those discovered by routine health control procedures 12.5 per cent. In the latter group were 26 males and only 5 females, and most of them were young. The age group 15 to 24 years dominated in the males. Twelve males were between 19 and 23 years old and were diagnosed by examinations of military conscripts or industrial employees; 17 of the 26 males were younger than 35 and 22 were younger than 50 years. Of the 5 females the oldest was 32 years.

2. *Distribution according to extent of pulmonary lesions*

The extent of the pulmonary lesions at diagnosis in the initially active cases is correlated in table 18 to the primary reasons for diagnosis. As could be expected, the number of patients who sought advice for symptoms of pulmonary tuberculosis as a rule increased as the extent of the disease progressed. Of the males whose primary symptom

Table 18. *Active Control Cases: Primary Reasons for Seeking Advice and Extent of Lesions*

Advice primarily sought for	Initial extent of lesions																				Males plus females	
	Minimal I		Minimal II		Moderately advanced		Far advanced		Total		Minimal I		Minimal II		Moderately advanced		Far advanced		Total			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	Males										*Females*											
Symptoms of pulmonary tuberculosis:																						
Haemoptysis			1	5.9	7	15.2	11	20.0	19	15.1	3	17.6			3	9.1	7	14.9	13	10.7	32	12.9
Cough			1	5.9	6	13.0	7	12.7	14	11.1			1	4.0	2	6.1	12	25.5	15	12.3	29	11.7
Cough, pyrexia, with or without night-sweats	2	25.0	2	11.8	2	4.3	14	25.6	20	15.9			3	12.0	7	21.2	19	40.4	29	23.8	49	19.8
Pyrexia with or without night-sweats					2	4.3	2	3.6	4	3.2	1	5.9	2	8.0	3	9.1	1	2.1	7	5.7	11	4.4
Pleurisy-type pain	1	12.5	2	11.8	4	8.7	4	7.3	11	8.7	1	5.9	3	12.0	2	6.1	2	4.3	8	6.6	19	7.7
Tiredness							3	5.4	3	2.4	1	5.9	1	4.0	1	3.0	1	2.1	4	3.3	7	2.8
Other diseases:																						
Nonpulmonary tuberculosis	2	25.0	1	5.9	3	6.6	2	3.6	8	6.3	5	29.4	6	24.0	6	18.2	3	6.4	20	16.4	28	11.3
Nontuberculous disease	1	12.5	1	5.9	2	4.3	6	10.9	10	7.9			1	4.0	4	12.1			5	4.1	15	6.0
Fortuitous findings:																						
Tuberculosis contacts			6	35.3	2	4.3	3	5.4	11	8.7	5	29.4	6	24.0	4	12.1	1	2.1	16	13.1	27	10.9
Examination for health certificate, national service, etc.	2	25.0	3	17.6	18	39.1	3	5.4	26	20.6	1	5.9	2	8.0	1	3.0	1	2.1	5	4.1	31	12.5
Total	8		17		46		55		126		17		25		33		47		122		248	

was cough alone, similar numbers had moderately and far advanced tuberculosis: But, if one adds the cases in which cough was accompanied by pyrexia with or without night-sweats, a profound difference appears — 17.3 per cent in the moderately advanced and 38.3 per cent in the far advanced cases. In the cases detected at examination for nonpulmonary tuberculous manifestations, the stage of the pulmonary disease was more evenly distributed. In the few cases discovered at examination for nontuberculous disease, the males with far advanced tuberculosis formed the largest group (6 cases). Seventeen of the 27 cases discovered by examination of tuberculosis contacts had minimal tuberculosis. In the cases found by routine health control investigations, the stages of pulmonary tuberculosis were evenly distributed in the 5 females. Of the 26 men, 18 had moderately advanced tuberculosis. Ten of the 18 were between 19 and 23 years old. Two others in this age group had far advanced tuberculosis.

3. *Discussion*

To illustrate further the composition of the control material, the cases were grouped according to the symptom or other reason which directly led to the discovery of pulmonary tuberculosis. There is reason to believe this series to be representative of tuberculosis in Sweden at the time in question. A report from the Swedish sanatorium of Orup may be cited for comparison. This report comprised *Fürst*'s (1952) observations concerning first hospitalizations during the period 1946 to 1950, a total of 883 patients. As 86.7 per cent of the cases with active tuberculosis in my control series were hospitalized, the series is well comparable with that of *Fürst*. The following figures show the reasons for seeking medical care in the two case materials.

	Fürst	Own series
Acute and/or general symptoms	42.4 %	45.2 %
Haemoptysis	7.9 %	12.0 %
Nontuberculous disease	8.6 %	7.5 %
Examination of tuberculosis contacts	11.0 %	10.6 %
Other dispensary activities	30.1 %	24.7 %

No county-wide radiographic investigation had then been made in the county from which *Fürst*'s series was collected. His somewhat higher figure for "other dispensary activities" would seem to be explained by tuberculosis discovered at group surveys. Otherwise the frequencies are strikingly similar in the two studies.

CHAPTER VIII

FOLLOW-UP PROCEDURE

1. *Clinical methods*

The follow-up period ended in January, 1957. The length of observation thus ranged from at least 8 to more than 10 years, or until pulmonary tuberculosis was considered to be cured, or until death. The start of observation in each case was the date when pulmonary tuberculosis was diagnosed by miniature or ordinary roentgenogram.

Persons who left Södermanland County were followed up in their new place of residence, even when several moves were made. By kind assistance from tuberculosis dispensaries, sanatoriums and other hospitals and from public registrars' offices, I obtained addresses to, and information and roentgenograms of such persons. The few who did not present themselves for examination at the end of follow-up were questioned by letter in regard to their health and working capacity. It was thereby ascertained that all the persons who had not been freed from supervision on medical grounds were still alive at the end of the observation period. The only exceptions were 8 emigrants from Sweden, and no more than 2 of these had been registered as tuberculous persons.

As is usual in dispensary supervision for tuberculosis, the patients were examined at intervals whose length was determined mainly by medical factors. In this follow-up investigation the results of such examinations were collectively assessed as one roentgenographic and one bacteriologic status per patient per year.

The *annual roentgenographic status* in each patient was evaluated in relation to the status in the preceding year. Progression and regression were each classified in three grades and unaltered status was separately registered.

Progression was denoted as follows:

+ = fresh, noncavitary parenchymal lesions which were small in relation to the lesions present in the preceding year. The size of the new lesions thus could vary somewhat, depending on the extent of the already existing disease,

+ + = more extensive, noncavitary parenchymal progression, and

+ + + = development of cavity, whether or not excavation was present in the preceding year.

Regression was denoted as follows:

— = disappearance of a small part of the parenchymal lesions,

— — = disappearance of a larger part of the lesions, and

— — — = disappearance of *all* pulmonary excavation.

Unchanged roentgenographic status, which also expressed relationship to the preceding year's findings, gave no information of the activity of the lesions.

During the year, several of the above-listed alternatives could, of course, occur in the same patient. The most unfavourable change in such cases was selected. If, for instance, a cavity appeared and disappeared in the same year, the progression (+ + +) was noted and the regression (— — —) was not recorded until the following year, even then only on condition that the lungs were quite free from excavation.

The *annual bacteriologic status,* on the other hand, was not evaluated in relation to results in the preceding year. The bacteriologic findings in each year were instead registered according to the scheme used for the initial status (table 13).

Treatment with specific drugs, hospitalization and pulmonary collapse or other interventions was noted. The records included the interval from diagnosis of pulmonary tuberculosis to commencement of treatment, complications and, when applicable, the duration of treatment and whether or not it was repeated.

Analysis of status after 8, 9 and 10 years was made from medical and economic aspects in the patients who then remained under dispensary supervision.

The *medical* results comprised evaluation of the activity of the pulmonary lesions. The classification used here was the same as for the status at diagnosis (chapter V), except that the designation "probably active" in the latter was replaced by "*unstable*" lesions. This was because the reason why the lesions could not be classed as definitely active was completely different in the retrospectively made evaluation of initial status and in these final assessments. The unstable cases had shown clear signs of activity in the three-year period immediately preceding the assessment 8, 9 or 10 years after diagnosis and, regardless of possible treatment during that period, their condition and history were such that the stability of healing was regarded as doubtful, although activity was not definitely present.

For *economic* assessment the patients were grouped as fit for full-time or part-time work or unfit for work, as long as they were less than 67 years old, i.e., the commencing age for old age pensions in this country. Disablement was further classed according to cause — tuberculosis or its sequelae, or other physical causes, or mental conditions.

In investigating *mortality* the causes of death, when they were not already known to the tuberculosis dispensary, were obtained from public registrars or from hospitals. All were attested by physicians.

2. *Statistical methods*

In a *planned experiment* that is deliberately designed to test the effect of a certain factor, an unbiased estimate requires avoidance of the influence of all other factors. For this a two-step procedure is employed. The first step involves control of all the accessible factors. The second comprises random allocation of the other known and of unrecognized factors to the various values of the factor under test.

Correlation between the test factor and the other accessible factors is avoided in classical experiments by keeping constant all but the test factor. The effect of the test factor then is the difference between groups with various values of this factor. In factorial experiments all the important factors are varied simultaneously but are kept uncorrelated. If the test factor's effect is independent of those of the other factors it will be expressed as the mean of the differences within pairs of groups which vary only with respect to the test factor or, simply, the difference between that part of the experimental material in which the test factor has one value and the part in which it has another. If the effect of the test factor is not independent of the other factors there is said to be interaction and the results must be somewhat differently evaluated.

Factorial experiments have two main advantages over classical experiments. They are more economical (the effect of a number of factors can be shown with the same precision from a factorial experiment of a size that, with the classical method, would illustrate only one factor's effect). Their results, being based on a more representative sample of the factors not under test, are more general (in classical experiments the results relate only to the special combination of "other" factors used).

The randomizing procedure should eliminate all other influence on the results. Correct randomization is therefore important for confidence in the statistical findings from an experimental investigation.

In results *not derived from a planned experiment* it is more difficult to estimate correctly the effect of a single factor. For instance, different factors of importance for the prognosis of a disease usually are closely correlated with each other. Direct comparison between that part of the material in which the factor has one value and the part in which it has another will as a rule give misleading results. For want of more appropriate methods, however, this procedure has been widely used in clinical work.

For reliable assessment of the prognostic significance of single factors, a clinical series must be so arranged that the relevant factor as far as possible is uncorrelated to other factors. This can be done by dividing the series into subgroups that differ only with respect to the factor under test and making comparisons between these subgroups. With suitable subdivision this method should be satisfactory if the series is very large (e.g., more than 10,000 cases). It has been used in some clinical work, but may not effectively utilize the material. Further, its effectiveness decreases as the number of subgroups increases, since some of the subgroups must then become too small for reliable results. The method is a parellel to a number of mutually unrelated planned experiments of the classical type.

In clinical series of, say, less than 10,000 cases, use of one of the described methods implies a choice between uncertain but relevant results from subgroups, or formally more certain but largely irrelevant results from undivided material.

For unbiased estimate of the effect of single factors with maximal effectiveness in use of the material, the following procedure was used in the *present study:*

1. *Division of the case material into subgroups homogenized with respect to the most important prognostic factors,*
2. *comparison between results in subgroups differering only as regards the factor under test, and*
3. *taking a weighted mean of these differences.*

In this way several uncertain comparisons between the alternatives of the test factor were combined into one reliable comparison relating to the total series.

The method gives relevant results and is a parallel to the factorial type of planned experiment. The results also are generally valid and can be more concisely presented than those obtained from methods which do not use weighted means.

As in a factorial experiment, interaction between the prognostic factors requires some modification of the analytic method. Tests of the present case material, however, revealed no significant interaction.

Whatever the statistical method used in the analysis, the results obtained from a set of clinical observations can never be quite so unchallengeable as those from a planned experiment. For this there are three main reasons.

The first is the impracticability of homogenizing a clinical series for all possible factors; nor can the chosen factors be divided into a great number of alternatives (the number of subgroups then would probably greatly exceed the number of cases). As a rule only 2 or 3 alternatives of each factor are manageable.

Secondly, the effects of some of the factors can scarcely be controlled or evaluated, since the value of these factors depends on the results in individual cases. For in-

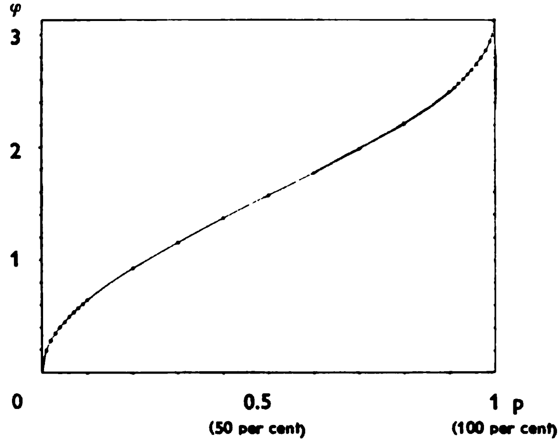


Fig. 10.
The function $\varphi = 2 \text{ arc sin} \sqrt{p}$ (after *Berlin*).

If the φ value is φ_1 and φ_2 in the 2 groups to be compared, then

$$\sigma^2_{\varphi_1} = \frac{1}{n_1} \qquad \sigma^2_{\varphi_2} = \frac{1}{n_2}$$

$$\sigma^2_{\varphi_1 - \varphi_2} = \frac{1}{n_1} + \frac{1}{n_2}$$

$$w = 1/\sigma^2_{\varphi_1 - \varphi_2} = \frac{1}{\frac{1}{n_1} + \frac{1}{n_2}} = \frac{n_1 \, n_2}{n_1 + n_2}$$

If Δ denotes the difference in φ values for a given factor, then $\Delta = \Sigma \omega_i \Delta_i / \Sigma \omega_i$, where $i = 1, 2, \ldots 8, 9$ if 9 pairs of values are tested. For the uncertainty in Δ, $\sigma_\Delta = 1/\sqrt{\Sigma w_i}$ is valid. In testing for significance,

$$t = \Sigma w_i \Delta_i / \sqrt{\Sigma w_i}$$

A difference of between 1.96 and 2.58 times the standard error is statistically *almost significant* ($0.01 < P \leqslant 0.05$); a difference of between 2.58 and 3.29 times the standard error is *significant* ($0.001 < P \leqslant 0.01$); a difference of 3.29 or more times the standard error is *highly significant* ($P \leqslant 0.001$). P denotes here the probability that different groups belong to the same population.

The difference in p values between pairs of subgroups as a rule is less when the p values are close to the limits 0 or 1 than when they are in the neighbourhood of 0.5. This is natural, since p cannot become less than 0 or more than 1. Values near the limits thus have less variability than values in mid-range. In many cases this discrepancy can give rise to significant interaction between two factors, with resultant complications in calculations and loss of precision.

The small variations at the extremes of the scale are enlarged when the φ transformation is used. The result then is that the differences between subgroups are more independent of the p values and interaction between the factors is definitely reduced. Nor was significant interaction demonstrated in the material of the present study.

The elongation of the φ scale at the ends also implies closer correspondence with the clinical value of the differences. For instance, a difference in mortality of 5 per cent must be regarded as more important when the rate of mortality is low than when it is about 50 per cent. With the φ transformation the difference at low mortality does, in fact, become the larger.

In order to use the function $\varphi = 2 \text{ arc sin } \sqrt{p}$ as effectively as possible, especially in small groups, a correction was made when none or all of the persons in a group showed unfavourable prognosis. This was done by substituting either $\frac{1}{4}n$ or $1-\frac{1}{4}n$ for p in the formula. The resulting function φ_B, which was introduced by *Bartlett* (1937), yields considerably better results in small statistical populations and in low and high frequencies than does the original function.

Eisenhart (1947) tested the efficiency of these functions under varying conditions. The following conclusions concerning the present study might well be drawn from his findings: The minimum requirement for efficient utilization of the function should be an expected value of at least 1 in at any rate the most important subgroups. If this criterion is not satisfied, the difference demonstrated, and the corresponding degree of significance, will be underestimated. The differences and significances then will accordingly be minimum values.

Example. The method used will now be exemplified.

The patients with elevated E.S.R. (from "borderline" readings to 40 mm/1 hour) and those with "nonpathologic" E.S.R. at diagnosis are compared with respect to unfavourable prognosis. The groups are heterogeneous as regards 2 factors which testing showed to be important for prognosis. These are roentgenographic extent of tuberculosis at diagnosis (3 groups) and age at diagnosis (3 groups). Consequently, the E.S.R. groups in table 19 are not directly comparable. To make the calculations independent of the mentioned correlations, the comparisons are made within 9 pairs of subgroups. Nine values are thereby obtained for the prognostic difference between the E.S.R. groups (table 20).

If the frequency figures in table 20 are converted to φ values (table 21), and the method described in the foregoing pages is used, we obtain:

$$\Delta = \Sigma w_i \Delta_i / \Sigma w_i = 11.004/82.438 = 0.133$$

$$\sigma_\Delta = 1/\sqrt{\Sigma w_i} = 1/\sqrt{82.438} = 1/9.080 = 0.110$$

$$t = \Sigma w_i \Delta_i / \sqrt{\Sigma w_i} = 11.004/9.080 = 1.206$$

$$\Delta = 0.133$$

$$\sigma_\Delta = 0.110$$

$t = 1.206$ Not significant

TABLE 19. *Roentgenographic Extent of Tuberculosis and Age at Diagnosis with Reference to E. S. R.*

Roentgenographic group	Age	E. S. R. Elevated No.	E. S. R. Elevated %	E. S. R. Nonpathologic No.	E. S. R. Nonpathologic %
Minimal	< 25	19	10.7	46	18.9
	25—49	21	11.9	78	32.1
	⩾ 50	8	4.5	4	1.6
Moderately advanced	< 25	15	8.5	14	5.8
	25—49	34	19.2	72	29.7
	⩾ 50	21	11.9	15	6.2
Far advanced	< 25	19	10.7	1	0.4
	25—49	24	13.6	9	3.7
	⩾ 50	16	9.0	4	1.6
	Total	177	100.0	243	100.0

TABLE 20. *Unfavourable Status at End of 8-Year Follow-up in Cases with Elevated and Cases with Nonpathologic E. S. R. at Diagnosis with Reference to Roentgenographic Extent of Tuberculosis and Age at Diagnosis*

Roentgenographic group	Age	Unfavourable results at end of 8 years (% of number in each subgroup; cf. table 19): E. S. R. Elevated No.	E. S. R. Elevated %	E. S. R. Nonpathologic No.	E. S. R. Nonpathologic %	Differences between groups with elevated and with nonpathologic E. S. R. %
Minimal	< 25	2	10.5	10	21.7	— 11.2 ± 9.3
	25—49	3	14.3	11	14.1	+ 0.2 ± 8.6
	⩾ 50	4	50.0	1	25.0	(+ 25.0)
Moderately advanced	< 25	4	26.7	1	7.1	+ 19.6 ± 13.3
	25—49	12	35.3	21	29.1	+ 6.2 ± 9.8
	⩾ 50	13	62.0	8	53.3	+ 8.7 ± 16.6
Far advanced	< 25	6	31.6	1	100.0	(— 68.4)
	25—49	17	70.8	2	22.2	+ 48.6 ± 16.6
	⩾ 50	14	87.5	4	100.0	(— 12.5)
	Total	75	42.4	59	24.3	+ 18.1 ± 4.6

TABLE 21. *Frequencies and Differences (Δ) from Table 20 Converted to φ Values. w = Weight of a Difference, n = Number of Cases*

Roentgenographic group	Age	E. S. R. Elevated n	Elevated φ	Nonpathologic n	Nonpathologic φ	Δ	w	Δw
Minimal	< 25	19	0.660	46	0.969	— 0.309	13.446	— 4.155
	25—49	21	0.776	78	0.770	0.006	16.545	0.099
	⩾ 50	8	1.571	4	1.047	0.524	2.667	1.398
Moderately advanced	< 25	15	1.086	14	0.539	0.547	7.241	3.961
	25—49	34	1.272	72	1.140	0.132	23.094	3.048
	⩾ 50	21	1.813	15	1.637	0.176	8.750	1.540
Far advanced	< 25	19	1.194	1	2.094	— 0.900	0.950	— 0.855
	25—49	24	2.000	9	0.981	1.019	6.545	6.669
	⩾ 50	16	2.419	4	2.638	— 0.219	3.200	— 0.701
						Total	82.438	11.004

The difference in the heterogeneous material (table 20) is highly significant.

Some differences are shown in brackets in table 20. The reason is that in 1 of the compared subgroups the total is less than 5 cases. The differences therefore are highly unreliable. The only difference in which any significance was found between subgroups concerned patients with far advanced tuberculosis who were 25 to 49 years old. Testing with an exact method showed this difference to be almost significant.

In 2 of the subgroups with nonpathologic E.S.R. and far advanced tuberculosis (younger than 25 and 50 or over) all the patients had unfavourable prognosis. In table 21, therefore, the relevant φ values are not stated as π (3.142), but are given according to *Bartlett's* correction.

Subdivision of the material. In the calculations with homogenized material the number of subgroups was limited to 72 ($2 \times 3 \times 4 \times 3$). Further subdivision would have made the subgroups very small and many of them would have been blank. In the preliminary analysis, however, some factors were studied in further subdivision (6 roentgenographic groups and 12 E.S.R. groups).

Another reason for limiting as far as possible the number of alternatives for each prognostic factor was that as the number of alternatives increases the degree of precision falls, since only a minor part of the material is

utilized in each comparison. For instance, with 6 alternatives only one-third of the material is used.

The calculations with homogenized material were made in 2 stages. First, the effects of all the factors were calculated, using 72 subgroups. It was thereby found that, with respect to total unfavourable prognosis and eight year mortality, the mass survey and control cases (except, of course, concerning differences between these cases) could be treated as a single material. The results in chapter IX E thus derive from calculations on 36 ($3 \times 4 \times 3$) subgroups. It was likewise found that, as regards first year mortality, the age groups (with corresponding reservation), could be combined, so that only 24 ($2 \times 3 \times 4$) subgroups were used in the final calculations.

By means of such combinations uncertainty resulting from excessively small groups can be considerably reduced. The results from the analyses with combined groups were practically identical with those obtained from 72 subgroups, indicating that the uncertainty mentioned was not of major importance in this study.

Confidence intervals. As the function $\varphi = 2 \text{ arc sin} \sqrt{p}$ has a constant variance that is independent of the frequency, the intergroup differences can be shown in diagrams in which the confidence intervals are equal for the varying frequencies of the respective prognostic categories. The confidence intervals are marked by interrupted lines. The diagrams therefore directly show the degree of significance of the differences between the compared groups.

Differences calculated by conventional methods were converted to φ values in order to permit direct comparisons. The confidence intervals in the 2 methods differ only very slightly in all calculations and in some cases are practically identical. For simplicity, therefore, the confidence intervals shown are those for the homogenized material.

The example in tables 19 to 21 shows that the results from the 2 methods may be fundamentally different (cf. table 38 and diagram).

χ^2 test. In the clinical section of the presentation of results differences in frequency were tested with the chi-square test, using Yates' correction for continuity (*Snedecor* 1956).

3. *Discussion*

In the follow-up investigation I elected to study the changes in roentgenographic status, the bacteriologic findings and therapy during the observa-

tion period, and to review the medical and economic results after 8, 9 and 10 years. The roentgenographic status for each year was judged in relation to the previous year's status. It would have facilitated the study if each year's status could, instead, have been consigned to a definite group using, for instance, some modification of the NTA definitions. So that even slight progression or regression would entitle to transfer, however, very many subgroups would have been required. Such an abundance of subdivisions would have made the material unmanageable.

The heterogeneity of the case material made it desirable to complement the clinical analysis of prognosis with a statistical investigation which would take into account the mutual dependency of various factors which were important for prognosis. It is known that some factors cannot be detached from their relationship with other factors for comparative analysis with conventional statistical methods. In recent years, however, the "homogenization method" has been evolved for statistical analysis of clinical observations. This method makes allowance for the association between the influence of different factors. *Welander* (1955) and *Strindberg* (1956) published odontologic studies and *Berlin* (1957) analyzed the prognosis in exudative pleurisy with homogenization techniques. *Berlin* and his statistical collaborator *Ek* showed that, by further development of given principles, it was possible not only to surmount the difficulties of heterogeneity but also to increase analytic precision, simplify calculations and present the results clearly in diagrammatic form. For the present study *Ek* also placed his services at my disposal.

CHAPTER IX

RESULTS OF FOLLOW-UP

1. *Tuberculosis active at diagnosis — initially active*

This investigation comprised the 339 mass survey cases and the 248 control cases which retrospective review showed to have had active pulmonary tuberculosis at the time of diagnosis. During the total observation period — up to 10 years — 20 of the patients from the mass survey group and 15 from the control group died of other causes than pulmonary tuberculosis. These cases are presented in table 22. In each series there was 1 death following surgery performed for tuberculous affection, and in the mass survey series a patient died of tuberculous meningitis after good regression of the pulmonary lesions had occurred in association with artificial pneumothorax.

A. **Roentgenographic progression and regression and tuberculosis mortality**

The 18 patients from the mass survey series and the 14 controls who died of other causes than pulmonary tuberculosis before the end of *8 years* (i. e., the period for which the total series could be followed up), the 5 persons from the mass survey group who were still registered but were not examined after 8 years, and the 2 survey patients who emigrated were excluded from the statistical treatment of 8-year prognosis according to the homogenization method. They were therefore also excluded from the following account of roentgenographic progression and regression, except as regards the annual frequency of these changes, when all cases were included for as long as they were examined.

Progression and regression of pulmonary tuberculosis thus were studied from two angles. In the first investigation, the *qualitative analysis,* each case could appear no more than once in each respect, viz., showing the highest grade of progression and the extreme of regression observed during 8 years. Thus, if + + + and + + were recorded in the same case, the former was selected, and — — was given preference over —.

TABLE 22. *Deaths from Other Causes than Pulmonary Tuberculosis in "Initially Active" Cases*

Sex	Age at diagnosis (years)	Pulmonary lesions at diagnosis	Survival after diagnosis (years)	Pulmonary tuberculosis at death	Cause of death
Mass survey					
Male	61	min. II	< 1	active	cardiovascular disease
»	47	mod. adv.	9—10	»	chronic nephritis
»	53	» »	3—4	»	cardiovascular disease
»	61	» »	6—7	»	» »
»	69	» »	5—6	»	» »
»	69	» »	4—5	unknown	» »
»	78	» »	2—3	»	» »
»	25	» »	2—3	active	operation for mixed-infection empyema
»	63	» »	< 1	»	bronchogenic cancer
»	52	far adv.	3—4	»	extrathoracic cancer
»	59	» »	8—9	»	cardiovascular disease
»	71	» »	7—8	»	chronic nephritis
Female	66	min. II	3—4	probably inactive	cardiovascular disease
»	63	mod. adv.	1—2	active	» »
»	73	» »	6—7	probably inactive	» »
»	65	far adv.	< 1	active	» »
»	74	» »	1—2	»	» »
»	34	min. I	1—2	»	septicaemia
»	22	min. II	1—2	»	tuberculous meningitis
»	65	mod. adv.	1—2	probably active	extrathoracic cancer
Controls					
Male	67	mod. adv.	5—6	probably active	cardiovascular disease
»	71	» »	< 1	active	» »
»	60	far adv.	9—10	unknown	» »
»	62	» »	2—3	active	» »
»	71	» »	< 1	»	» »
»	82	» »	< 1	»	» »
»	35	min. II	3—4	probably inactive	accident
»	54	» »	2—3	probably active	chronic nephritis
»	50	mod. adv.	7—8	inactive	myeloma
»	25	far adv.	< 1	active	bleeding after open pneumonolysis
»	41	» »	< 1	»	suicide
Female	75	min. I	1—2	unknown	cardiovascular disease
»	16	min. II	3—4	probably active	extrathoracic cancer
»	67	mod. adv.	1—2	» »	» »
»	42	far adv.	4—5	active	perforated gastric ulcer

For the qualitative analysis the cases were divided according to roentgenographic status at diagnosis into the following 6 modified NTA groups. The detailed composition of these groups may be studied in *table 5.*

M I	= minimal I	subgroups	A and B
M II	= minimal II	»	C to F
MA I	= moderately advanced I	»	G to J
MA II	= moderately advanced II	»	K to O
FA I	= far advanced I	»	P and Q
FA II	= far advanced II	»	R to T

The 5 cases of fatal pulmonary tuberculosis in which time did not permit roentgenographic examination (see p. 31) were also included in the last group.

The results of the qualitative analysis are presented in figure 11 and table 23. The number of cases in each of the 6 roentgenographic groups is shown in the table.

Progression with excavation (+ + +) appeared in all 6 groups in both the mass survey and the control series. Of the patients with minimal tuberculosis at diagnosis, a not inconsiderable number later developed cavitary tuberculosis; 22 (16.9 per cent) of the total of minimal cases in the mass survey series and 7 (11.1 per cent) of the corresponding control cases progressed to excavation. Of the cases with moderately advanced tuberculosis when first seen, about 30 per cent in the mass survey and in the control group showed progression + + +. In the far advanced cases this frequency was 65 to 70 per cent. Chi-square tests failed to reveal any significant difference between corresponding roentgenographic groups of mass survey and control cases as regards cavitary progression. Study of figure 11 and table 23 shows that, on the whole, progression in this analysis was similarly distributed in the survey series and in the controls.

As regards roentgenographic *regression* it is pertinent to point out that by definition moderately advanced II and far advanced II tuberculosis are cavitary states, and that of the far advanced I groups 45 per cent in the mass survey series and 52 per cent in the control series had cavitary lesions at the outset. Under favourable circumstances, therefore, a high frequency of disappearance of all cavities (— — —) should occur in these cases. Because of the large numbers with progression, often fatal, in the far advanced groups, such regression frequency was not found in them. In moderately advanced II, on the other hand, the survey and the control cases both differed strikingly from the other roentgenographic groups, in that cavitary clearance occurred in 67.7 per cent of the survey group and in 76.9 per cent of the control group. In this connection it should be

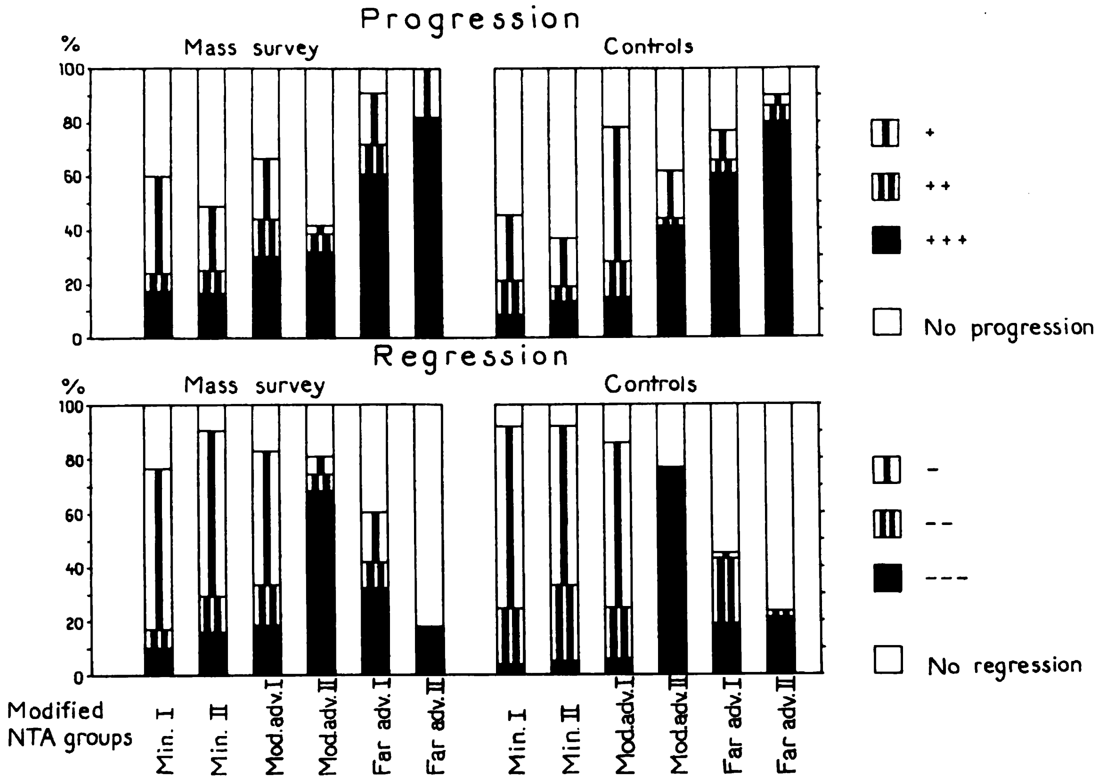


Fig. 11. »Qualitative» roentgenographic progression and regression during 8-year observation period.

TABLE 23. *"Qualitative" Roentgenographic Progression and Regression during 8-year Observation Period*

	Roentgenographic groups and number of cases																							
	Mass survey												Controls											
	M I (58)		M II (72)		MA I (99)		MA II (31)		FA I (43)		FA II (11)		M I (24)		M II (39)		MA I (36)		MA II (39)		FA I (46)		FA II (50)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Progression																								
+	21	36.2	17	23.6	22	22.2	1	3.2	8	18.6	2	18.2	6	25.0	7	17.9	18	50.0	7	17.9	5	10.9	2	4.0
++	4	6.9	6	8.3	14	14.1	2	6.5	5	11.6			3	12.5	2	5.1	5	13.9	1	2.6	2	4.3	3	6.0
+++	10	17.2	12	16.7	30	30.3	10	32.2	26	60.5	9	81.8	2	8.3	5	12.8	5	13.9	16	41.0	28	60.9	40	80.0
Total	35	60.3	35	48.6	66	66.7	13	41.9	39	90.7	11	100.0	11	45.8	14	35.8	28	77.7	24	61.5	35	76.1	45	90.0
Regression																								
—	34	58.6	44	61.1	49	49.5	2	6.5	8	18.6			16	66.7	21	53.8	22	61.1			1	2.2		
— —	4	6.9	10	13.9	15	15.2	2	6.5	4	9.3			5	20.8	13	33.3	7	19.4			11	23.9	1	2.0
— — —	6	10.3	11	15.3	18	18.2	21	67.7	14	32.6	2	18.2	1	4.2	2	5.1	2	5.6	30	76.9	9	19.6	11	22.0
Total	44	75.9	65	90.3	82	82.8	25	80.6	26	60.5	2	18.2	22	91.7	36	92.3	31	86.1	30	76.9	21	45.7	12	24.0

observed that artificial pneumothorax was given to a much greater extent in moderately advanced II tuberculosis than in any other group, and usually resulted in rapid cavitary closure.

In the cases which by definition were noncavitary at diagnosis, viz., the minimal groups and moderately advanced I, the frequency of regression — — — was relatively low. During the 8-year period it was less than the frequency of cavitary progression. The patients who were responsible for this difference either died while cavitation was present or still had cavitary lesions at the end of observation.

In the second investigation of the roentgenographic changes, the *quantitative analysis,* each year's observations were included. The individual patients therefore appeared each time they showed progression or regression. The *degree* of the change was disregarded in this analysis. The roentgenographic groups were regarded as single units whose improvement or worsening was denoted by the number of cases with progression or regression during a year in per cent of the number examined in the same year. As the number of observed cases successively diminished, the 6 roentgenographic groups used in the qualitative analysis were combined into the usual 3 NTA groups of minimal, moderately advanced and far advanced tuberculosis.

The annual progression and regression rates are shown in figure 12. When a group comprised less than 10 cases the curve was interrupted. The curves for *progression* are seen to be mainly similar in the mass survey groups and in the control groups. The only difference of note concerned progression during the first year of observation in the far advanced cases. The controls here showed the high frequency of 65.3 per cent, as against 39.3 per cent in the mass survey group. This difference was statistically highly significant ($\chi^2 = 8.6$ $0.001 < P < 0.005$).

The distribution of roentgenographic *regression,* like that of progression, was similar in the roentgenographic groups of both series. An exception was the high frequency of regression in the far advanced survey cases in the eighth and ninth observation years. The number of such cases under observation in the latter year was 25 and of these 9 showed regression. Eight of the 9 had far advanced I lesions at diagnosis and regression was associated with pulmonary resection in 3 of them and with thoracoplasty in 1.

This investigation therefore showed that when the clinical material was divided according to extent of tuberculosis at diagnosis, roentgenographic progression and regression, quantitatively calculated, occurred on the whole with similar frequency in the cases discovered by mass survey and in the control cases. The most important difference was in the frequency of progression in far advanced tuberculosis in the first year of observation.

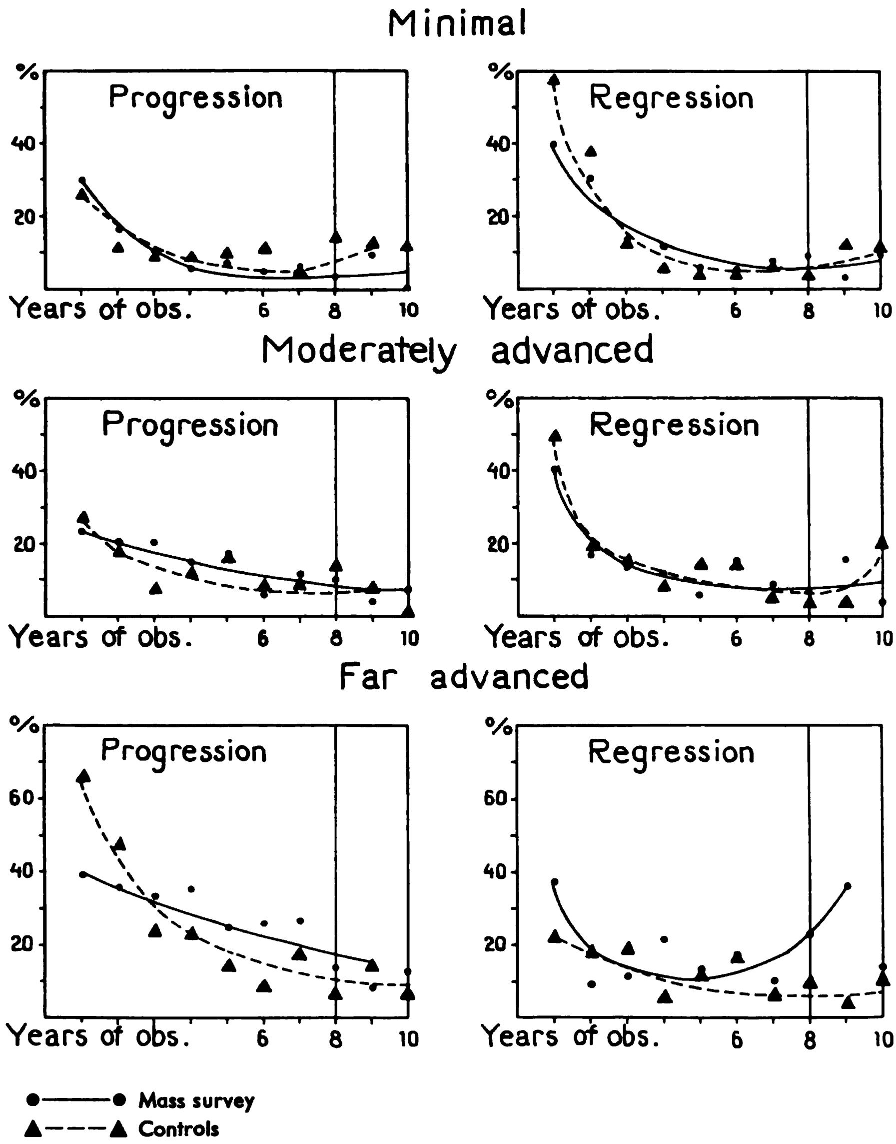


Fig. 12. »Quantitative» roentgenographic progression and regression in each year of observation period.

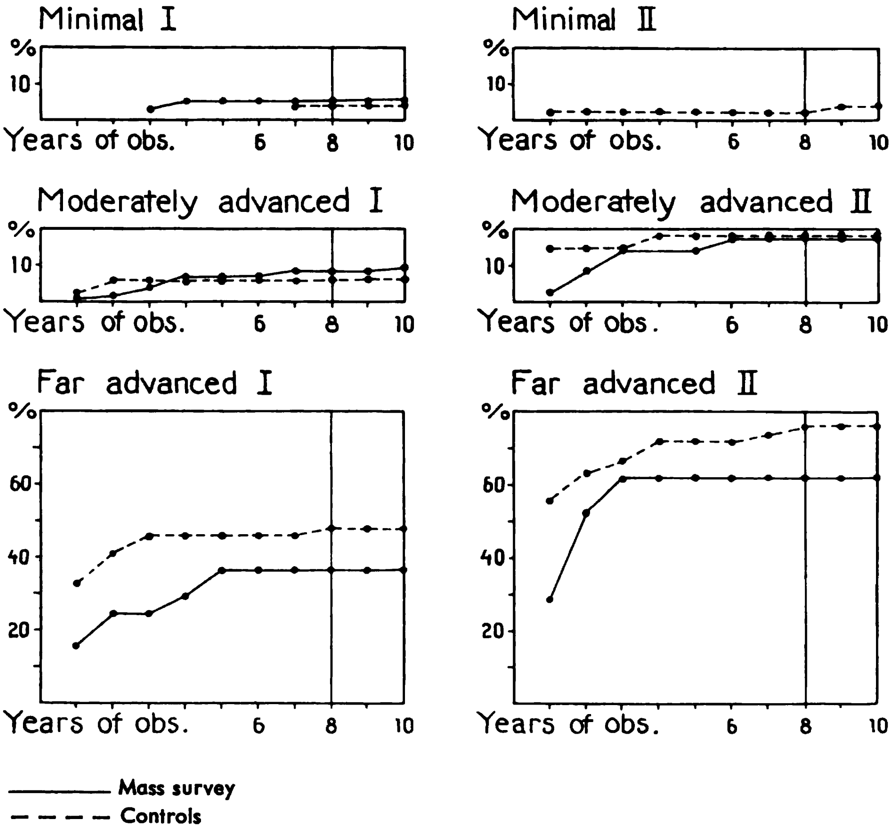


Fig. 13. **Deaths from pulmonary tuberculosis. Cumulative calculation of annual risk in roentgenographic groups.**

The *mortality risk* from pulmonary tuberculosis was calculated for each year in each of the 6 modified NTA groups. It was expressed as the number of patients dying per year of pulmonary tuberculosis in per cent of the number at risk at the beginning of the year, i. e., the group total reduced by deaths from all causes before that year; the 2 emigrants were also deducted when they were lost to observation. The annual risk was then cumulated according to the formula

$$P = 1 + (1 - p_1)\ (1 - p_2)\ (1 - p_3)\ .\ .\ .$$

in which P denotes the total risk after a certain number of years, and p_1 the risk during the first year, and so on.

Figure 13 and table 24 present the cumulative risk of dying from pulmonary tuberculosis in each of the 6 modified NTA groups of the mass survey and the control series. Mortality is seen to have been low in the

TABLE 24. *Cumulative Risk of Death from Pulmonary Tuberculosis*

Year of obs.	*Cumulative mortality risk (per cent)* — Roentgenographic groups					
	M I	M II	MA I	MA II	FA I	FA II
	Mass survey					
1			0.9	2.8	15.9	28.6
5	5.1		6.6	14.3	36.6	61.9
8	5.1		7.7	17.4	36.6	61.9
10	5.1		8.6	17.4	36.6	61.9
	Controls					
1		2.4	2.6	15.0	32.7	56.0
5		2.4	6.2	18.5	45.7	72.2
8	4.2	2.4	6.2	18.5	48.1	76.2
10	4.2	4.9	6.2	18.5	48.1	76.2
Year of obs.	*No. at risk at beginning of year* — Roentgenographic groups					
	M I	M II	MA I	MA II	FA I	FA II
	Mass survey					
1	60	78	107	36	44	14
5	55	75	96	29	30	4
8	55	74	94	25	27	4
10	55	74	94	25	26	3
	Controls					
1	25	42	39	40	52	50
5	24	38	36	32	24	14
8	23	38	35	32	23	13
10	23	37	34	32	22	12

2 minimal groups and in moderately advanced I. In the moderately advanced II group in both series the total mortality risk was about 18 per cent: The difference in the first year was not statistically significant. In moderately advanced I and II together, however, there was a statistically almost significant difference ($\chi^2 = 5.5$ $0.010 < P < 0.025$). In the far advanced groups there was an obvious discrepancy as regards tuberculosis mortality in the first year of observation and some difference persisted throughout the observation period. Thus, in far advanced I

and II together, deaths from pulmonary tuberculosis in the first year amounted to 18.9 per cent in the mass survey cases and 44.1 per cent in the control cases. The difference was highly significant ($\chi^2 = 9.2$ $0.001 < P < 0.005$).

The deaths from pulmonary tuberculosis in the patients who had minimal disease at diagnosis merit brief comment. Of those classed as minimal I, 3 in the mass survey group and 1 in the control group died. Of the fatal survey cases 1 was a 60-year-old woman with a strong family history of tuberculosis. She and the second patient, a 46-year-old man, were mentally ill. The E. S. R. at diagnosis was high in the woman but was not measured in the man. Both died in the third year of observation. The third fatal case was a 63-year-old man with severe polyarthritis, who died in the fourth year, when he was found also to have genito-urinary tuberculosis. His E. S. R. was not measured at diagnosis. The single control case with minimal I lesions when first seen was a 13-year-old girl with much familial tuberculosis who, despite bilateral artificial pneumothorax and antimicrobial therapy, died in the seventh year of observation. Her E. S. R. was 26 mm/1 hour at diagnosis.

Of the patients with minimal II tuberculosis on the initial films, 2 controls died. Both were men about 20 years old. One showed progression ++ in the second year but refused examination and treatment until the sixth year. After several cavitary progressions he died in the ninth year. His E. S. R. was normal at diagnosis. The other man had high E. S. R. when first seen and the disease progressed to a fatal conclusion within a year. Artificial pneumothorax and phrenic crush were performed.

Apart from the highly significant difference in the far advanced cases and the almost significant difference in the moderately advanced cases in the first year of observation, with greater frequency in the control group, mortality from pulmonary tuberculosis was essentially similar in the roentgenographic groups of the cases discovered by mass survey and in those of the control cases.

B. Bacteriologic studies

As shown earlier (table 13) tests for tubercle bacilli were made in the great majority of the patients in association with diagnosis of tuberculosis. Of the initially active cases only 26 of those in the mass survey series and 14 in the control series, i.e. 7.7 and 5.6 per cent, respectively, were not bacteriologically examined at diagnosis. That such examination was carried out later in most of these cases is seen from table 25. During an observation period of 8 years only 7 of the mass survey cases and 6 of the

Table 25. *Interval from Diagnosis to Bacteriologic Studies in Active Cases Not Initially Examined*

Interval between diagnosis and initial bacteriologic studies	No. of cases		Remarks							
			Declined examination		Mentally ill or deficient		Primary lung lesions		Other cases	
	Mass survey	Controls	Mass survey	Controls	Mass survey	Controls	Mass survey	Controls	Mass survey	Controls
<1 year . . .	7	3			1				6	3
1—2 years . .	3								3	
2—4 » . .	4	2	1	1	2				1	1
4—8 » . .	5	3	3	2	1				1	1
No examination	7	6	3		1		2	4	1	2
Total	26	14	7	3	5		2	4	12	7

Table 26. *Bacteriologic Findings during Observation Period in Initially Active Cases*

	Results of bacteriologic tests						
	Initially positive	Initially negative		Initially no test		All cases	
		Total	Later positive	Total	Later positive	Total	Positive within 8 years
Mass survey:							
Males . .	83 (48.5 %)	76	29 (17.0 %)	12	8 (4.7 %)	**171**	120 (70.2 %)
Females . .	72 (42.9 %)	82	25 (14.9 %)	14	7 (4.2 %)	**168**	104 (62.0 %)
Males plus females .	155 (45.7 %)	158	54 (15.9 %)	26	15 (4.4 %)	**339**	224 (66.0 %)
Controls:							
Males . .	87 (69.0 %)	32	13 (10.3 %)	7	3 (2.4 %)	**126**	103 (81.7 %)
Females . .	67 (54.9 %)	48	17 (13.9 %)	7	2 (1.6 %)	**122**	86 (70.4 %)
Males plus females .	154 (62.1 %)	80	30 (12.1 %)	14	5 (2.0 %)	**248**	189 (76.2 %)

The figures in brackets denote % of the total for the sex within the group (mass survey or control) or, respectively, % of the group total.

controls were not bacteriologically studied. The table also presents some explanatory data in these cases. For the examined cases the interval between diagnosis and bacteriologic testing is shown.

The totals of cases with positive bacteriologic findings initially or in a follow-up period of 8 years are given in table 26. Of those whose initial tests were negative for tubercle bacilli, about one-third in the mass sur-

vey series and also in the control series had positive tests later. These "later positives" comprised 15.9 and 12.1 per cent of the respective series. For the cases not initially studied, but in which tubercle bacilli were demonstrated in the follow-up period, the corresponding figures were 4.4 per cent of the mass survey series and 2.0 per cent of the controls. In all, 66.0 per cent of the initially active cases in the mass survey and 76.2 per cent of those in the control group had tests positive for tubercle bacilli at some time during the 8-year period. Positive findings were more common in males than in females in both series. This difference was not unexpected, in view of the higher frequency of advanced tuberculosis in the males (table 5).

C. Treatment

Of the control series, 86.7 per cent and of the mass survey series 71.4 per cent of the initially active cases received *hospitalization* for pulmonary tuberculosis at some time during the observation period. In figure 14 is shown the time between diagnosis of tuberculosis and first admission to hospital. It is evident that hospital care was given more frequently and somewhat earlier to the control cases than to the survey cases. Also the duration of first hospitalization was somewhat longer in the control cases (fig. 15).

Hospitalization was repeated once or oftener in 27.1 per cent of the mass survey cases and in 33.3 per cent of the controls. These later periods, too, tended to be longer in the control cases than in the survey cases (fig. 16).

When the mass radiographic survey was begun, *specific medication* was very rarely given for tuberculosis, and even towards the end of the three-year period specific drugs could be given only to relatively strictly selected cases. To illustrate the part played by this medication in the prognostic comparison between mass survey and control cases, the interval from diagnosis to commencement of medication was recorded in each case. As shown in figure 17, specific medication was begun soon after diagnosis rather oftener in the control material than in the survey cases. This circumstance probably arose from the larger number of control cases with advanced pulmonary tuberculosis with or without spread to the larynx or the intestines. The commencing percentages are small in both series, however. Thus, in the first trimester after diagnosis only 3 patients — all from the control material — and between 3 and 6 months only 5 controls and 3 survey cases received specific drugs. In the first year after diagnosis 11 control cases and 8 survey cases, or 4.4 and 2.4 per

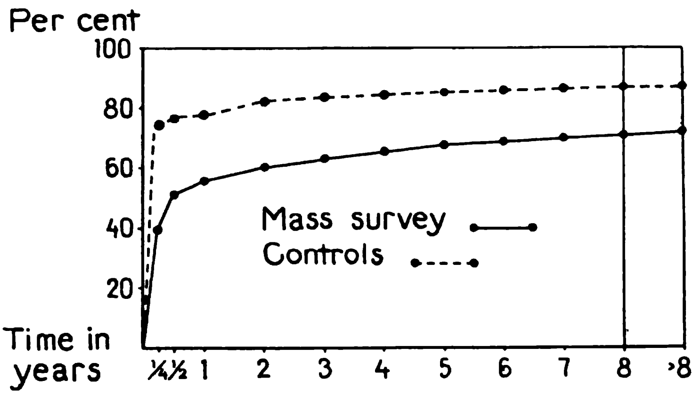


Fig. 14. **First hospitalization for pulmonary tuberculosis. Number of cases admitted within various intervals after diagnosis. Calculated in % of total mass survey cases (339) and total controls (248) and cumulated.**

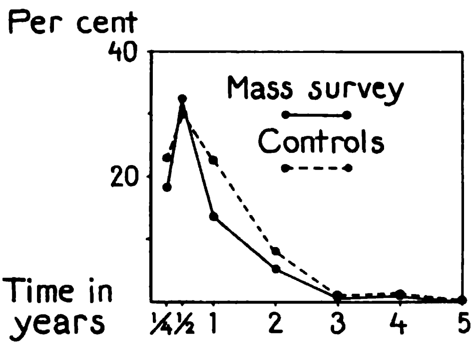


Fig. 15. **Duration of first hospitalization for pulmonary tuberculosis (% of total in group).**

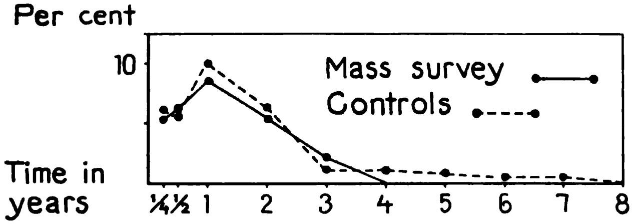


Fig. 16. **Total duration of second and later hospitalizations for pulmonary tuberculosis (% of total in group).**

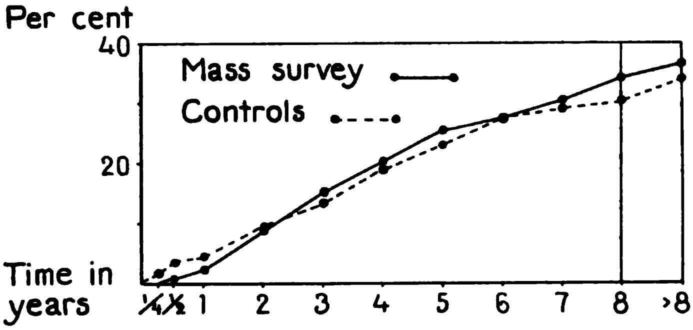


Fig. 17. **First course of antituberculosis medication. Number of cases treated within various intervals after diagnosis. Calculated in % of total mass survey cases (339) and total controls (248) and cumulated,**

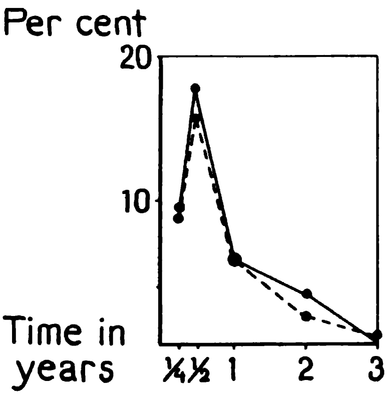


Fig. 18. **Duration of first course of antituberculosis medication (% of total in group).**

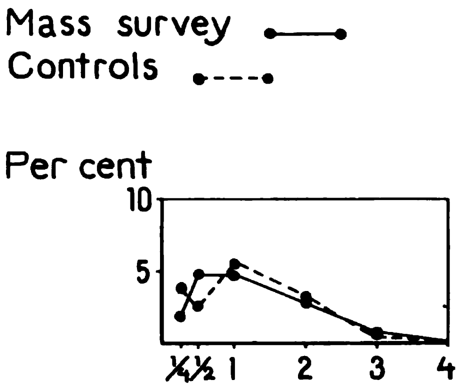


Fig. 19. **Total duration of second and later courses of antituberculosis medication (% of total in group).**

cent of the active cases in the respective groups, had begun specific medication.

As with hospitalization, the mass survey and control cases were compared as regards the duration of the first period of specific medication (fig. 18) and the sum of subsequent periods (fig. 19). The series were strikingly similar in these respects.

At the time from which the cases were collected, the most common of the *active therapeutic measures* in pulmonary tuberculosis was artificial intrapleural pneumothorax.

TABLE 27. *Quality of Collapse in Artificial Intrapleural Pneumothorax*

	Mass survey (339 cases) No.	%	Controls (248 cases) No.	%
No space found	26	7.7	19	7.7
Pneumothorax abandoned within 6 months	7	2.1	5	2.0
Pneumothorax maintained at least 6 months	86	25.3	81	32.7
Unilateral collapse	74	21.8	65	26.3
Bilateral collapse	12	3.5	16	6.4
Satisfactory collapse	56	16.5	38	15.3
Unsatisfactory collapse	30	8.8	43	17.4
thereof with persistent cavity	6	1.8	17	6.9

Intrapleural *pneumothorax* was counted as such only when collapse was maintained for at least 6 months. In table 27 the patients with intrapleural pneumothorax are grouped according to whether collapse was unilateral or bilateral, and satisfactory or unsatisfactory. Satisfactory pneumothorax was considered to have existed when collapse had been maintained for at least 3 years and a selective effect was achieved. Medial pleural adhesions up to clavicle level did not preclude satisfactory pneumothorax unless the situation of the lesions was such that even medial adhesions prevented the desired effect. If a patient died before the end of the 3-year period his pneumothorax was regarded as satisfactory if the other conditions were fulfilled. Of the unsatisfactory pneumothoraces those with persistent cavity are shown as a special group in table 27.

Intrapleural pneumothorax was maintained for less than 6 months in 2.1 per cent of the mass survey cases and in 2.0 per cent of the controls. They are excluded from the following presentation as are, of course, the cases in which no space was found; these constituted 7.7 per cent of both series.

In the total control material intrapleural pneumothorax was more common (32.7 per cent) than in the total survey series (25.3 per cent). Notwithstanding, unsatisfactory pneumothorax was recorded in 17.4 per cent of the control series as compared with 8.8 per cent of the survey series (table 27). As the percentage of cases in which pneumothorax was unsuccessfully attempted was equal in both series, I have interpreted the above-mentioned differences as due to a somewhat greater need of pulmonary collapse in the control group, a need which could not be fully met, however, because of the greater tendency to complications of active therapy in this group. That pleural adhesions tended to be more frequent is indicated by the higher figures for pleurisy in the anamneses of the

TABLE 28. *Type and Frequency of Active Therapy*

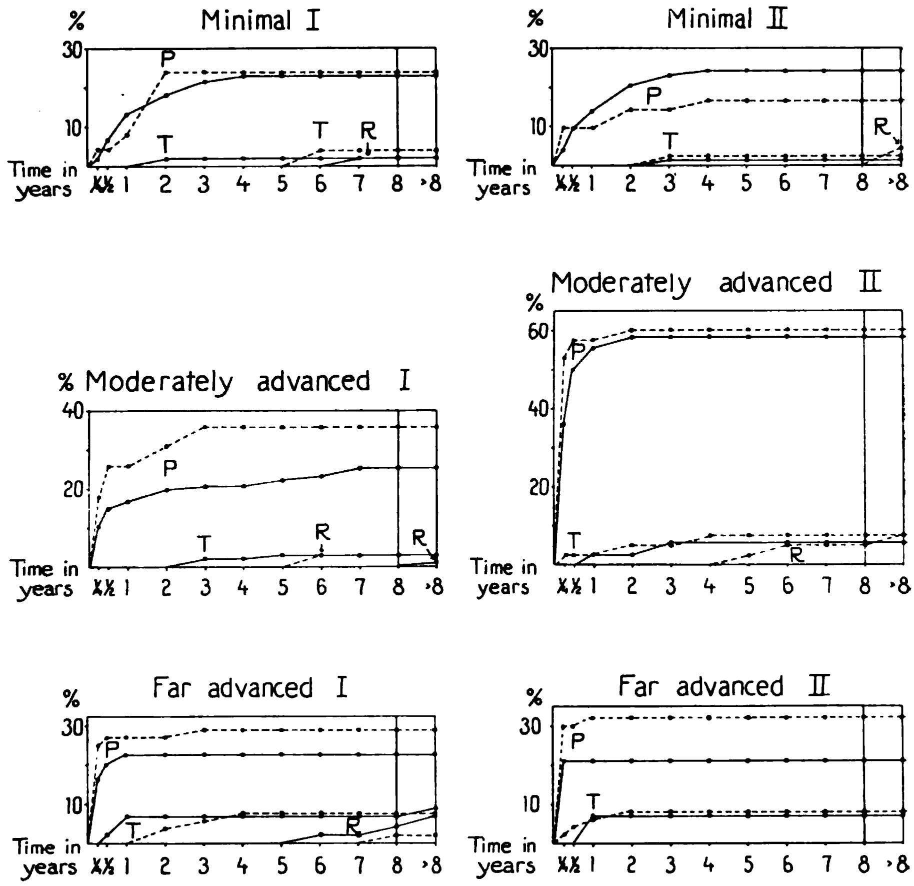
Roentgeno-graphic group	Mass survey							Controls						
	No. of cases	Pneumo-thorax No.	Pneumo-thorax %	Thoraco-plasty No.	Thoraco-plasty %	Resec-tion No.	Resec-tion %	No. of cases	Pneumo-thorax No.	Pneumo-thorax %	Thoraco-plasty No.	Thoraco-plasty %	Resec-tion No.	Resec-tion %
Min. I	60	14	23.3	1	1.7	1	1.7	25	6	24.0	1	4.0		
Min. II . . .	78	19	24.4	1	1.3			42	7	16.7	1	2.4	2	4.8
Mod. adv. I .	107	27	25.2	3	2.8	1	0.9	39	14	35.9			1	2.6
Mod. adv. II .	36	21	58.3	2	5.6			40	24	60.0	3	7.5	3	7.5
Far adv. I . .	44	10	22.7	4	9.1	3	6.8	52	15	28.9	4	7.7	1	1.9
Far adv. II. .	14	3	21.4	1	7.1			50	16	32.0	4	8.0		

control cases (table 11) and also for pleural complications when the pulmonary disease was diagnosed (table 15). Other factors, dependent on the higher frequency of advanced tuberculosis in the control material, may likewise be presumed to have influenced the choice of therapy and the incidence of complications.

As the indications for artificial pneumothorax presumably varied greatly according to the extent of the tuberculous disease and the presence or absence of excavation, the clinical material was divided for study of the frequency of pneumothorax by cleavage of each of the 3 groups of the NTA classification (see p. 30). This division into 6 groups was further motivated by the uneven distribution of the extent of tuberculosis in the survey cases and in the control material, with preponderance of advanced cases in the latter (table 28).

As pneumothorax cases were counted, in addition to intrapleural pneumothorax which was maintained for at least 6 months, 8 mass survey cases and 1 control case with extrapleural pneumothorax.

Figure 20 shows the frequency of pneumothorax in the 6 modified NTA groups and also the interval between diagnosis of tuberculosis and induction of pneumothorax. The highest frequency of pneumothorax was in the group with moderately advanced II tuberculosis at diagnosis. Approximately 60 per cent of this group in the survey and in the control series were treated with pneumothorax. This finding was not surprising, as such cases on the one hand were more accessible to treatment than were the far advanced cases, and on the other hand implied stronger indications for collapse therapy than did noncavitary tuberculosis, viz., minimal I and II and moderately advanced I. In moderately advanced I and in far advanced I and II tuberculosis the control groups received more pneumothorax treatment than did the corresponding survey groups.



———— Mass survey
– – – – Controls
P = artificial pneumothorax
T = thoracoplasty
R = pulmonary resection

Fig. 20. **Active treatment of pulmonary tuberculosis. Number of cases treated within various intervals after diagnosis. Calculated in % of roentgenographic group in mass survey or control series (see table 28) and cumulated.**

In minimal II the survey cases showed some preponderance in this respect, and in minimal I the frequency of pneumothorax was similar in both series.

Thoracoplasty was performed in 12 cases in the mass survey series of initially active tuberculosis and in 13 of the active control cases.

TABLE 29. *Complications of Active Therapy*

	Number of cases	
	Mass survey	Controls
Number of active therapeutic measures	**111**	**102**
Complications		
Seropneumothorax	34	41
Tuberculous empyema	1	5
Nontuberculous empyema	2	1
Bronchopleural fistula	2	3
Intrathoracic bleeding	1	1
Total complications	40	51
in % of active measures	**36.3**	**50.0**

Pulmonary resection was almost never undertaken for tuberculosis at the time of the mass survey. In my material the first resection operation was performed in the fifth year of observation. Five of the mass survey series and 7 of the controls underwent pulmonary resection of varying extent.

These major surgical procedures are also shown in figure 20. The total frequencies of pneumothorax, thoracoplasty and pulmonary resection in the 6 modified NTA groups are shown in table 28.

The *complications* of the active therapeutic procedures are seen in table 29. Seropneumothorax was counted as such only when it rose above the dome of the diaphragm or was present in corresponding amount as "riding" effusion. During the period in question seropneumothorax was a more frequent occurrence than after specific medication came into wider use. That it was more common in the control cases than in the survey cases may be ascribed to the larger number of cases with unsatisfactory pneumothorax in the controls and also to the preponderance of far advanced tuberculosis in that group. Tuberculous empyema was likewise more common in the controls than in the survey cases.

Complications followed 36.3 per cent of the interventions in the mass survey series and exactly half of those in the control series.

D. Clinical analysis of results after 8, 9 and 10 years

In the foregoing sections of this follow-up investigation, roentgenographic progression and regression, tuberculosis mortality and frequency of active therapeutic measures were studied with the clinical material divided according to roentgenographic extent of tuberculosis at diagnosis. In the present section, which concerns the long-term medical and economic results,

TABLE 30. *Clinical Results 8 Years after Diagnosis (all initially active cases)*

Clinical results	Mass survey						Controls					
	Males		Females		Males plus females		Males		Females		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Dead of pulmonary tuberculosis	21	12.3	20	11.9	41	12.1	34	27.0	39	32.0	73	29.4
Dead of other causes	10	5.8	8	4.8	18	5.3	10	7.9	4	3.3	14	5.6
Still on tuberculosis register	121	70.8	92	54.8	213	62.8	66	52.4	52	42.6	118	47.6
Removed from register, lesions healed	18	10.5	47	28.0	65	19.2	16	12.7	27	22.1	43	17.3
Emigrated from Sweden	1	0.6	1	0.6	2	0.6						
Total	171		168		339		126		122		248	

the cases detected by mass survey and the control cases are presented as undivided series. Such presentation permits a good general conception of what the mass survey of Södermanland County implied as a complement to the routine activities of the tuberculosis dispensary. In the next section — the statistical treatment of 8-year prognosis — a return is made to classification according to initial roentgenographic status, in order to assist in the statistical analysis of the clinically demonstrated prognostic differences between the survey series and the control series.

Of the patients with active tuberculosis at diagnosis there *remained on the register after 8 years* 213 of the mass survey series and 118 of the control series. Table 30 shows these cases and also the reasons why observation ceased in the other cases. It is seen that 12.1 per cent of the mass survey group and 29.4 per cent of the control group died of pulmonary tuberculosis. There were no major sex differences in this respect. Death from other causes than pulmonary tuberculosis occurred in rather more than 5 per cent of both groups. The proportion of cases removed from the register because of healing of tuberculosis was also highly similar, viz., 19.2 per cent of the mass survey series and 17.3 per cent of the control series. In both series the frequency of healed tuberculosis was manifestly higher in females than in males, and this was inversely reflected in the sex distribution of the cases remaining on the register. These differences between the sexes were associated with greater frequency of advanced tuberculosis at diagnosis in the males of both series (table 5).

At the end of 8 years 70.8 per cent of the males and 54.8 per cent of the females in the mass survey series were still under supervision for pulmonary tuberculosis. The corresponding figures in the control cases were

TABLE 31. *Medical Status after 8 Years in Initially Active Cases Still on Tuberculosis Register*

Status of pulmonary tuberculosis	Mass survey						Controls					
	Males		Females		Males plus females		Males		Females		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Active	25	20.7	8	8.7	33	15.5	13	19.7	7	13.5	20	16.9
Unstable	25	20.7	16	17.4	41	19.2	17	25.8	7	13.5	24	20.3
Probably inactive	37	30.6	33	35.9	70	32.9	15	22.7	16	30.8	31	26.3
Inactive	31	25.6	33	35.9	64	30.0	21	31.8	22	42.3	43	36.4
Not examined	3	2.5	2	2.2	5	2.3						
Total	121		92		213		66		52		118	

52.4 and 42.6 per cent. Calculated from the totals of both sexes, 62.8 per cent of the survey cases and 47.6 per cent of the controls were still registered. This difference, however, is not by itself indicative of the prognosis. It must be viewed in the light of the considerably higher mortality from pulmonary tuberculosis in the control series, which in turn was attributable to the preponderance of advanced disease in that series.

The *medical status after 8 years* of observation in the patients who then remained on the tuberculosis register is shown in table 31. Active or unstable tuberculosis after 8 years was more common in the male patients than in the females and, conversely, the latter predominated in the inactive and probably inactive groups. Thus, in the survey series as well as in the controls, more than 40 per cent of the males but only about 26 per cent of the females were in the first two, prognostically unfavourable groups. In the total figures for each series, however, this difference according to sex was levelled out, and the sum of active and unstable cases was 34.7 per cent in the mass survey series and 37.2 per cent in the control group.

A summary of the medical results after 8 years in all the initially active cases minus patients who died of other causes than pulmonary tuberculosis, or who emigrated or, although they were still registered, were not examined in the eighth year, is presented in table 32. Two categories of prognosis are distinguished. The first is *satisfactory 8-year prognosis,* viz., removal from the tuberculosis register as cured, or still registered but with inactive or probably inactive tuberculosis. The second category, *unsatisfactory 8-year prognosis,* comprises persons who died of pulmonary tuberculosis, or who survived 8 years but still had active or unstable

Table 32. *Summary of Medical Results 8 Years after Diagnosis in Initially Active Cases*[1]

Medical results	Mass survey						Controls					
	Males		Females		Males plus females		Males		Females		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Satisfactory												
Lesions healed, inactive or probably inactive . .	86	54.8	113	72.0	199	**63.4**	52	44.8	65	55.1	117	**50.0**
Unsatisfactory												
Dead of tuberculosis, or lesions active or unstable	71	45.2	44	28.0	115	**36.6**	64	55.2	53	44.9	117	**50.0**
Total	157		157		314		116		118		234	

[1] Excluding patients dead of other causes than pulmonary tuberculosis, patients still on register but not examined, and emigrants.

lesions. According to this calculation, half of the control material and somewhat more than one-third of the mass survey material had unsatisfactory prognosis; the difference was statistically significant — chi-square value 9.3 $0.001 < P < 0.005$. That most of this difference was ascribable to the highly significant preponderance of mortality from tuberculosis in the controls (26.4 $P < 0.001$) is apparent from the similarity between the two series in other prognostic respects (tables 30 and 31).

In many of the patients who were still on the tuberculosis register 8 years after diagnosis the observation period was not long enough for analysis of 9-year prognosis. For study after *9 years* there remained 55.9 per cent of the mass survey patients and 85.6 per cent of the controls who comprised the groups still registered after 8 years. The difference between these percentages reflects the earlier average time of diagnosis for the control material.

The *medical status after 9 years* of the patients who were still registered then or whose names were deleted from the register during the ninth year of observation is presented in table 33. Since, as mentioned, many of the cases still registered at the end of 8 years were not observed for longer than that time, direct comparison between 9-year and 8-year results was not feasible. I have therefore chosen to compare the medical findings as regards 9-year prognosis with the status of the same individuals at the end of the 8-year period. For this purpose two groups of status were

TABLE 33. *Cases Followed Up for 9 Years. Medical Status after 9 Years*

Cases observed 9 years, status at end of 8 years	No. of cases	Pulmonary tuberculosis after 9 years				Dead	
		Active or unstable	Inactive or probably inactive	Healed	Not examined	Tuberculosis	Other causes
Lesions active or unstable							
Mass survey . . .	45	39 (86.7 %)	5 (11.1 %)				1 (2.2 %)
Controls	37	30 (81.1 %)	5 (13.5 %)		1 (2.7 %)	1 (2.7 %)	
Lesions inactive or probably inactive							
Mass survey . . .	69	3 (4.3 %)	48 (69.6 %)	17 (24.6 %)	1 (1.4 %)		
Controls	64	4 (6.2 %)	44 (68.7 %)	14 (21.9 %)	2 (3.1 %)		
Not examined							
Mass survey . . .	5	1			4		

TABLE 34. *Cases Followed Up for 10 Years. Medical Status after 10 Years*

Cases observed 10 years, status at end of 9 years	No. of cases	Pulmonary tuberculosis after 10 years				Dead	
		Active or unstable	Inactive or probably inactive	Healed	Not examined	Tuberculosis	Other causes
Lesions active or unstable							
Mass survey . . .	8	5 (62.5 %)	1 (12.5 %)			1 (12.5 %)	1 (12.5 %)
Controls	23	19 (82.6 %)	4 (17.4 %)				
Lesions inactive or probably inactive							
Mass survey . . .	21		16 (76.2 %)	4 (19.0 %)	1 (4.8 %)		
Controls	25		22 (88.0 %)	3 (12.0 %)			
Not examined							
Mass survey . . .	1				1		
Controls	3				2		1

used, one comprising active or unstable tuberculosis and the other inactive or probably inactive tuberculosis.

Of the cases with active or unstable lesions after 8 years, 5 from the mass survey series and 5 from the controls were classed as probably inactive after 9 years, while fully 80 per cent remained in the former group. Of the cases with inactive or probably inactive tuberculosis after 8 years, 3 from the mass survey series and 4 from the controls were worse at the end of 9 years and 24.6 per cent of the survey cases and 21.9 per cent of the control cases were deleted from the register as cured: In about 70 per cent of both series the 8-year classification still applied after 9 years.

Five survey cases and 3 control cases were not examined in the ninth year; 4 of the former had also defaulted the previous year. In the ninth year there was 1 death from pulmonary tuberculosis in the control series and 1 death from cardiovascular disease in the survey series.

The 2 series of cases thus displayed highly similar behaviour from the eighth to the ninth year of observation.

Of the participants in the 9-year analysis, 25.2 per cent of the mass survey group and 50.5 per cent of the control group were followed up for *10 years* or were removed from the register during the tenth year. The *medical status after 10 years* in these cases is presented in table 34. In each series 2 persons had not presented themselves for examination. In the mass survey series 2 patients died in the tenth year, 1 of them from pulmonary tuberculosis. In the control group there was a death from cardiovascular disease in the same year. The findings 10 years after diagnosis were likewise compared with the same patients' status at the end of the foregoing year.

Although the mass survey cases seemed to show somewhat better prognosis than the control cases after 10 years, the small numbers, particularly in the survey group, do not permit reliable conclusions in this respect.

The 213 cases from the mass survey series and the 118 controls still registered 8 years after diagnosis were further assessed as regards *economic status*. In this connection one must keep in mind the dividing line which I have drawn at 67 years, the age at which general old age pensioning begins in Sweden. For persons aged 67 years or over, classification according to fitness for work was not appropriate and therefore they were grouped according to activity of pulmonary tuberculosis. This gives some idea of that part of the physical capacity which was reduced or eliminated by pulmonary tuberculosis.

The *economic status after 8 years* is shown in table 35. Of the persons who then were younger than 67 and were still registered, two-thirds were *fit for full-time work* in the mass survey series as well as in the control series. In both series, there was an appreciable and similar female prepon-

Table 35. *Economic Status after 8 Years in Initially Active Cases Still on Tuberculosis Register*

Economic status	Mass survey						Controls					
	Males		Females		Males plus females		Males		Females		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Younger than 67 years:												
In full-time work	72	59.5	72	78.2	144	67.6	40	60.6	39	75.0	79	66.9
In part-time work	10	8.3	3	3.3	13	6.1	9	13.6	5	9.6	14	11.9
Unfit for work												
Tuberculosis	15	12.4	5	5.4	20	9.4	11	16.7	7	13.5	18	15.3
Mental disorder	13	10.7	5	5.4	18	8.5	1	1.5			1	0.8
Other causes	2	1.7	1	1.1	3	1.4	2	3.0	1	1.9	3	2.5
No information			1	1.1	1	0.5						
Total	112	92.6	87	94.5	199	93.4	63	95.4	52	100	115	97.5
67 or older:												
Tuberculosis inactive or probably inactive	1	0.8	2	2.2	3	1.4						
Active or unstable	6	5.0	2	2.2	8	3.8	3	4.5			3	2.5
Activity unknown	2	1.7	1	1.1	3	1.4						
Total	9	7.5	5	5.5	14	6.6	3	4.5			3	2.5
Grand total	121		92		213		66		52		118	

derance in this respect; about 75 per cent of females were fit for full-time work, as against about 60 per cent of the males. The criteria, however, were of necessity somewhat more strict for men, as care of the home was regarded as full-time work for women. Of course, the greater number of male patients with advanced disease at diagnosis also influenced these figures. Persons whose pulmonary tuberculosis rendered them only *fit for part-time work* comprised 6.1 per cent of the survey series and 11.9 per cent of the control series. *Unfit for work* because of pulmonary tuberculosis or its sequelae were 9.4 per cent of the survey series and 15.3 per cent of the controls. A relatively small number were unfit for work for other reasons. In all such patients pulmonary tuberculosis was inactive or probably inactive. Patients who had both reasons for disablement were classed with the actively tuberculous unfit.

Of pensionable age were 14 patients from the mass survey group and 3 from the control group. Eight of these survey cases and all 3 of the controls had active or unstable pulmonary tuberculosis. Concerning 3 of the others from the survey group it was known only that the patients were alive and free from symptoms of the disease.

TABLE 36. *Summary of Economic Results 8 Years after Diagnosis in Initially Active Cases*[1]

Economic results	Mass survey						Controls					
	Males		Females		Males plus females		Males		Females		Males plus females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Satisfactory	116	73.4	130	82.8	246	**78.1**	68	58.6	72	61.0	140	**59.8**
Unsatisfactory	42	26.6	27	17.2	69	**21.9**	48	41.4	46	39.0	94	**40.2**
Total	158		157		315		116		118		234	

Satisfactory = removed from register as "cured",
still registered but fit for full-time or part-time work, or
disabled but not from pulmonary tuberculosis, or
$\geqslant$67 years old with inactive or probably inactive tuberculosis.
Unsatisfactory = dead of pulmonary tuberculosis,
lesions active or unstable,
$\geqslant$ 67 years old with active or unstable tuberculosis.

[1] Excluding patients dead of other causes than pulmonary tuberculosis, patients still on register but with unknown economic status, and emigrants.

A summary of the economic results after 8 years in the initially active cases, with reductions similar to those in the summary of medical status, is shown in table 36. Here, too, 2 prognostic categories were recognized. It is seen that economically *satisfactory 8-year prognosis* was found in 78.1 per cent of the mass survey cases, but in only 59.8 per cent of the control cases and that therefore the respective frequencies of *unsatisfactory 8-year prognosis* were 21.9 and 40.2 per cent. This difference was highly significant (χ^2 20.6 P $<$ 0.001). Comparison with table 32 shows that the economically satisfactory groups were larger than the medically satisfactory. This was because a number of patients with unstable or even active tuberculosis were nevertheless at work.

The *economic status after 9 and 10 years* is not presented in detail, as the findings added nothing of importance to the comparison after 8 years between the mass survey series and the controls.

From the foregoing, it is evident that the prognosis from medical and economic aspects was considerably better for the tuberculosis cases detected by mass radiographic survey than for the control cases, *when the two series were treated as single units.* In the statistical analysis which now follows, however, the medical results are studied with a method which takes into consideration the heterogeneity of these clinical series.

E. Statistical analysis of results after 8 years

The statistical analysis of homogenized and heterogeneous case material was made after the interval between diagnosis and follow-up which was common to *all* cases, i.e., 8 years.

From the material for statistical analysis were deducted the patients who died of other causes than pulmonary tuberculosis (table 22). They comprised 5.3 per cent of the cases detected by mass survey and 5.6 per cent of the control cases. Deducted from the mass survey series were also 2 persons who emigrated from Sweden and 5 who did not present themselves for examination after 8 years but were known to be subjectively well.

After extensive preliminary studies of the data noted in each case, it was found that 3 factors were of special importance from the prognostic aspect. These were the roentgenographic extent of tuberculosis, the E.S.R. and the age at diagnosis. With regard to sex, on the other hand, the preliminary studies showed that as such it had so little influence on prognosis that homogenization for sex was unnecessary.

Definitions

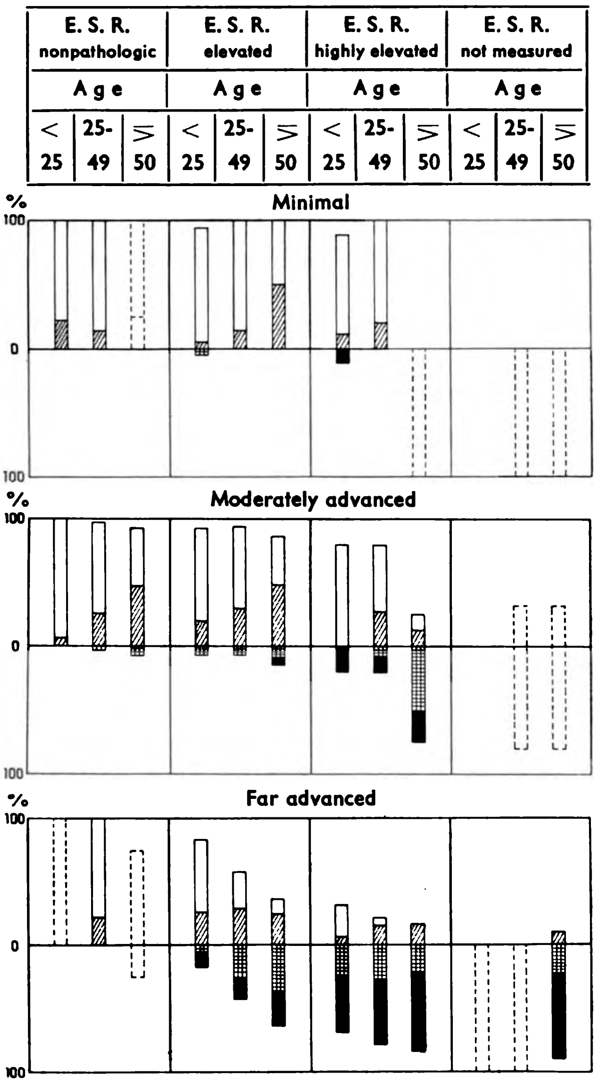
The following definitions were accepted for the 3 principal *prognostic factors.*

1. *Roentgenographic extent of tuberculosis* was classified according to the 3 groups of the NTA scheme, viz., *minimal, moderately advanced* and *far advanced.*
2. *E.S.R.* was also given 3 values: a) *nonpathologic* = normal or borderline readings, i.e. up to and including 10 mm/1 hour in men and 15 mm in women, b) *elevated* = from borderline readings to 40 mm, and c) *highly elevated* = more than 40 mm. In addition, there was a small group in which E.S.R. was not measured at diagnosis.
3. *Age* had as its 3 groups a) *younger than 25* years, b) *25 to 49* years, and c) *50 or older.*

All data in these respects refer to the time when pulmonary tuberculosis was diagnosed by mass radiography or other means.

The *eight year prognosis* was investigated from 3 aspects.

1. *Total unfavourable prognosis* = pulmonary tuberculosis still active or unstable at the end of 8 years or fatal during that period.
2. *Eight year mortality* = deaths from pulmonary tuberculosis during the 8 years.
3. *First year mortality* = deaths from pulmonary tuberculosis within 1 year of diagnosis.



Status after 8 years

Inactive or probably inactive

Active or unstable

Dead after 1—8 years

Dead within 1 year

Fig. 21. Influence of the 3 "prognostic factors" — roentgenographic extent of tuberculosis, E. S. R. and age at diagnosis — on the 8-year prognosis of active pulmonary tuberculosis in the combined mass survey and control series.
Values stated in % of the respective subgroups, with each subgroup representing 100 %.
Columns with interrupted outlines represent less than 5 cases.
Above the zero line the columns denote survivors after 8 years, and below this line deaths from pulmonary tuberculosis.

The importance of the principal prognostic factors in heterogeneous and in homogenized material

A schematic survey of the influence of the selected factors on prognosis is given in figure 21. Here the mass-survey detected cases and the control cases are combined and the total is divided into groups with respect to the above-mentioned factors. Within each group the eight year prognosis is shown.

The differences between the mass survey cases and the controls as regards distribution of the prognostic factors are presented in figure 22. Since the respective total series were of unequal size, the frequencies are stated in per cent of all survey cases or all controls. It is seen that, judged from the roentgenographic status and the E.S.R. at diagnosis, the control material as a whole was sicker than the survey material. With respect to age, the columns show that persons younger than 25 years were considerably more common among the controls, while the 25 to 49 age group predominated in the survey series, mainly as the result of high frequency among patients with mild lesions and nonpathologic E.S.R. The total of persons aged 50 years or over was similar in both series of cases, but this category showed a pronounced tendency to accumulate among the control cases with advanced tuberculosis and high E.S.R.

In the more detailed analysis of the prognostic factors which now follows, each factor is illustrated by 2 tables and a diagram.

In *table a* the unfavourable prognosis is shown from the 3 stated aspects with reference to the relevant prognostic factor. *Table b* shows the correlation between the factors studied. It illustrates the degree of heterogeneity as regards important prognostic factors between the groups compared in the accompanying *diagram*. The columns in the diagram express the prognostic differences between the stated values of the relevant prognostic factor. The blank columns represent differences in conventionally calculated, heterogeneous material, and the solid columns denote differences between homogenized groups.

In the diagrams the upper row of columns shows the differences between the upper and lower extremes of the prognostic factor, the middle row shows the differences between the highest and the middle group, and the bottom row the differences between the middle and the lowest value of the factor.

Roentgenographic extent of tuberculosis. The diagram to tables 37 *a* and *b* illustrates the prognostic differences between the 3 roentgenographic groups.

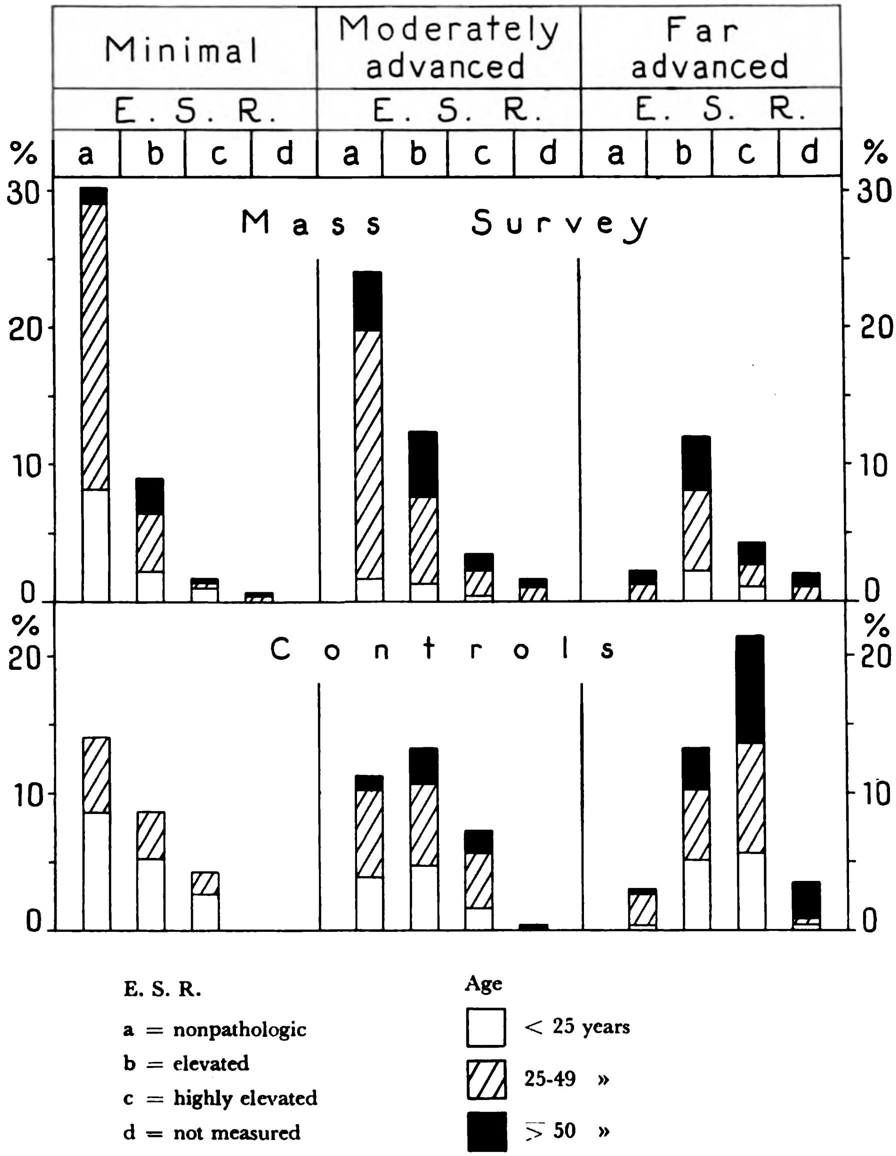


Fig. 22. **General distribution of the 3 "prognostic factors" — roentgenographic extent of tuberculosis, E. S. R. and age at diagnosis — in active mass survey cases and controls. Values stated in % of the total cases in the respective series.**

TABLE 37 a. *Unfavourable Status at End of 8-Year Follow-up of Active Pulmonary Tuberculosis with Reference to Roentgenographic Extent at Diagnosis. Heterogeneous Material (cf. table 37 b and diagram)*

Roentgeno-graphic group	No. of cases	Unfavourable results at end of 8 years					
		Tuberculosis active, unstable or fatal		Tuberculosis fatal			
				Within 8 years		Within 1 year	
		No.	%	*No.*	%	*No.*	%
Minimal . .	193	37	19.2	5	2.6	1	0.5
Mod. adv. .	205	80	39.0	23	11.2	9	4.4
Far adv. . .	150	115	76.7	86	57.3	56	37.3
Total	548	232	42.3	114	20.8	66	12.0

TABLE 37 b. *Mass Survey Cases and Controls, E. S. R. and Age at Diagnosis with Reference to Roentgenographic Extent of Disease at Diagnosis (relationship in %)*

Roentgeno-graphic group	No. of cases	Clinical material		E. S. R.				Age		
		Mass survey	Con-trols	Non-patho-logic	Ele-vated	Highly ele-vated	Not mea-sured	< 25	25—49	⩾ 50
Minimal . .	193	130	63	128	48	15	2	74	105	14
		67.4	**32.6**	**66.3**	**24.9**	**7.8**	**1.0**	**38.3**	**54.4**	**7.3**
Mod. adv. .	205	130	75	101	70	28	6	34	124	47
		63.4	**36.6**	**49.3**	**34.1**	**13.7**	**2.9**	**16.6**	**60.5**	**22.9**
Far adv. . .	150	54	96	14	59	63	14	37	61	52
		36.0	**64.0**	**9.3**	**39.3**	**42.0**	**9.3**	**24.7**	**40.7**	**34.7**
Total	548	314	234	243	177	106	22	145	290	113
		57.3	**42.7**	**44.3**	**32.3**	**19.3**	**4.0**	**26.5**	**52.9**	**20.6**

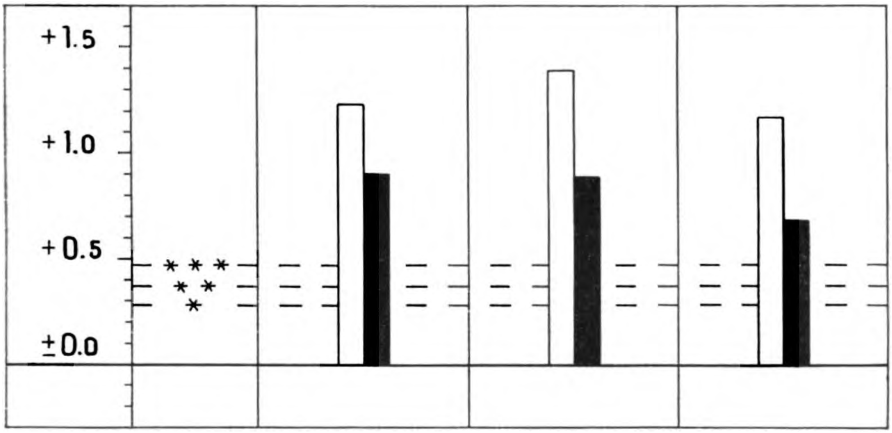
In the heterogeneous material far advanced tuberculosis entailed very much poorer prognosis from all aspects than did minimal disease. Appreciably less, but still very great, were the differences between far advanced and moderately advanced tuberculosis. All the differences were highly significant. Between moderately advanced and minimal tuberculosis, on the other hand, the differences were considerably less. They were highly significant as regards total unfavourable prognosis and eight year mortality and significant for first year mortality.

After homogenization the poorer prognosis in far advanced tuberculosis as compared with each of the other 2 groups was less pronounced than in the above comparison. The differences were still highly significant from all

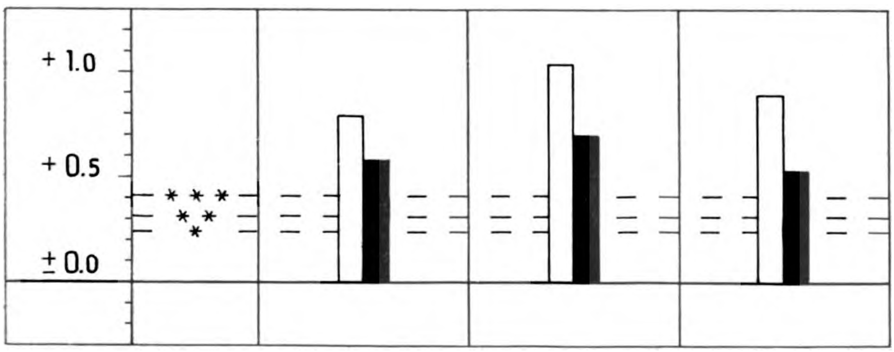
Diagram to Tables 37 a and b. *Differences Between Various Roentgenographic Groups in Heterogeneous* ☐ *and Homogenized* ■ *Material*

φ	Confidence intervals	Tuberculosis active, unstable or fatal	Tuberculosis fatal	
			Within 8 years	Within 1 year

Far advanced — Minimal



Far advanced — Moderately advanced



Moderately advanced — Minimal

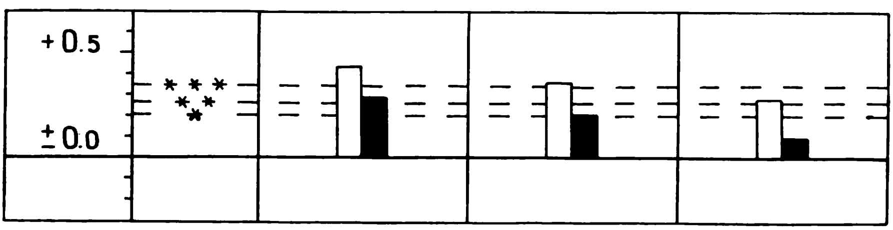


TABLE 38 a. *Unfavourable Status at End of 8-Year Follow-up of Active Pulmonary Tuberculosis with Reference to E. S. R. at Diagnosis. Heterogeneous Material (cf. table 38 b and diagram)*

E. S. R.	No. of cases	Unfavourable results at end of 8 years					
		Tuberculosis active, unstable or fatal		Tuberculosis fatal			
				Within 8 years		Within 1 year	
		No.	%	*No.*	%	*No.*	%
Nonpathologic .	243	59	24.3	4	1.6	1	0.4
Elevated	177	75	42.4	30	16.9	13	7.3
Highly elevated .	106	76	71.7	61	57.5	40	37.7
Not measured . .	22	22	100	19	86.4	12	54.5
Total	548	232	42.3	114	20.8	66	12.0

TABLE 38 b. *Mass Survey Cases and Controls, Roentgenographic Extent of Disease and Age at Diagnosis with Reference to E. S. R. at Diagnosis (relationship in %)*

E. S. R.	No. of cases	Clinical material		Roentgenographic group			A g e		
		Mass survey	Con-trols	Mini-mal	Mod. adv.	Far adv.	< 25	25—49	≥ 50
Nonpathologic . . .	243	177	66	128	101	14	61	159	23
		72.8	**27.2**	**52.7**	**41.6**	**5.8**	**25.1**	**65.4**	**9.5**
Elevated	177	95	82	48	70	59	53	79	45
		53.7	**46.3**	**27.1**	**39.5**	**33.3**	**29.9**	**44.6**	**25.4**
Highly elevated . .	106	29	77	15	28	63	30	44	32
		27.4	**72.6**	**14.2**	**26.4**	**59.4**	**28.3**	**41.5**	**30.2**
Not measured . . .	22	13	9	2	6	14	1	8	13
		59.1	**40.9**	**9.1**	**27.3**	**63.6**	**4.5**	**36.4**	**59.1**
Total	548	314	234	193	205	150	145	290	113
		57.3	**42.7**	**35.2**	**37.4**	**27.4**	**26.5**	**52.9**	**20.6**

prognostic aspects. Between moderately advanced and minimal tuberculosis the differences were comparatively small also in homogenized material and were less than in the heterogeneous material. The higher frequency of total unfavourable prognosis in the moderately advanced cases was significant and the difference in eight year mortality was almost significant, but the tendency in favour of the minimal cases as regards first year mortality lacked significance.

Diagram to Tables 38 a and b. *Differences Between Various E.S.R. Groups in Heterogeneous ☐ and Homogenized ■ Material*

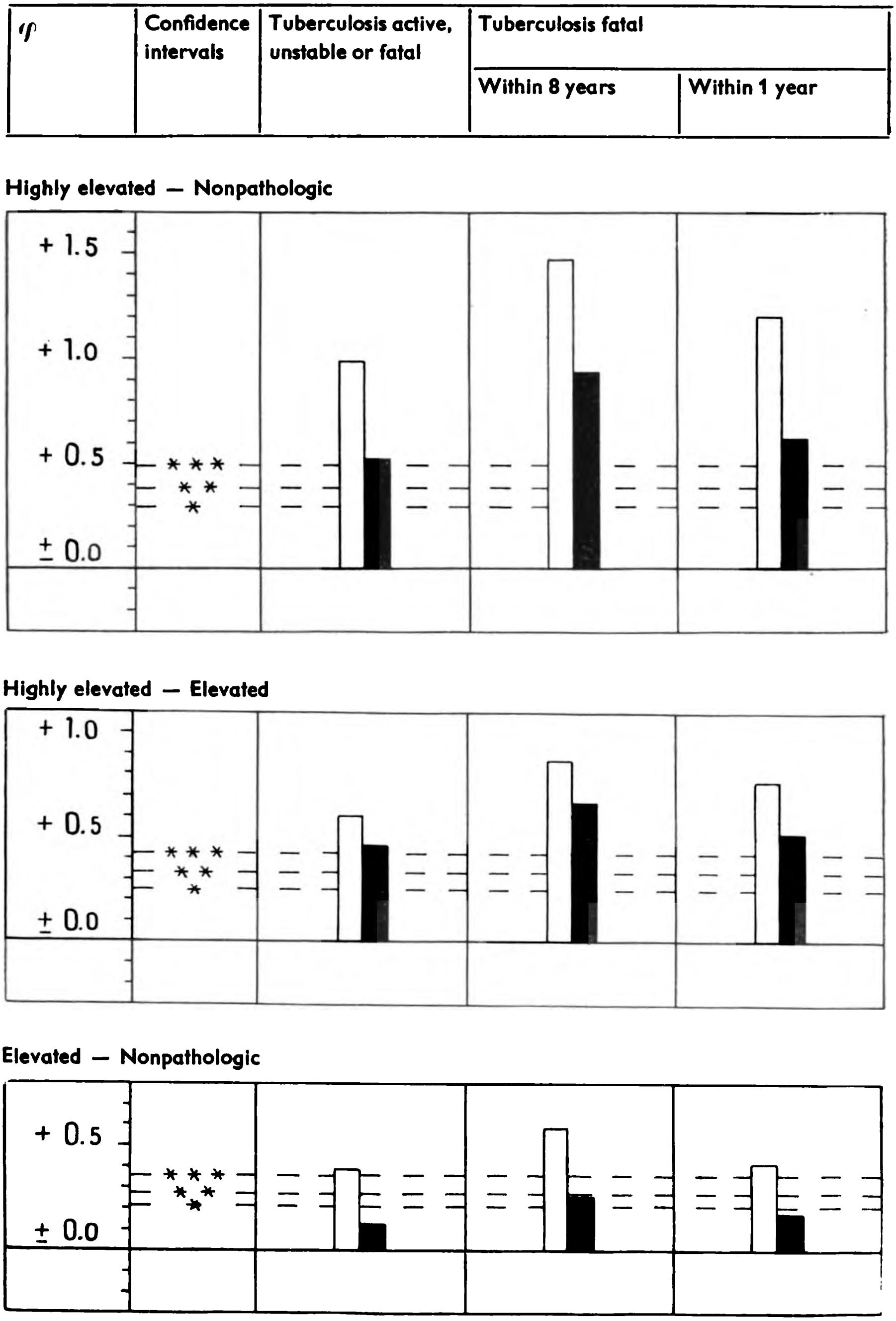


TABLE 39 a. *Unfavourable Status at End of 8 Year Follow-up of Active Pulmonary Tuberculosis with Reference to Age at Diagnosis. Heterogeneous Material (cf. table 39 b and diagram)*

Age	No. of cases	Unfavourable results at end of 8 years					
		Tuberculosis active, unstable or fatal		Tuberculosis fatal			
				Within 8 years		Within 1 year	
		No.	%	*No.*	%	*No.*	%
< 25	145	40	27.6	19	13.1	12	8.3
25—49 . . .	290	105	36.2	43	14.8	25	8.6
≥ 50	113	87	77.0	52	46.0	29	25.7
Total	548	232	42.3	114	20.8	66	12.0

TABLE 39 b. *Mass Survey Cases and Controls, Roentgenographic Extent of Disease and E. S. R. at Diagnosis with Reference to Age at Diagnosis (relationship in %)*

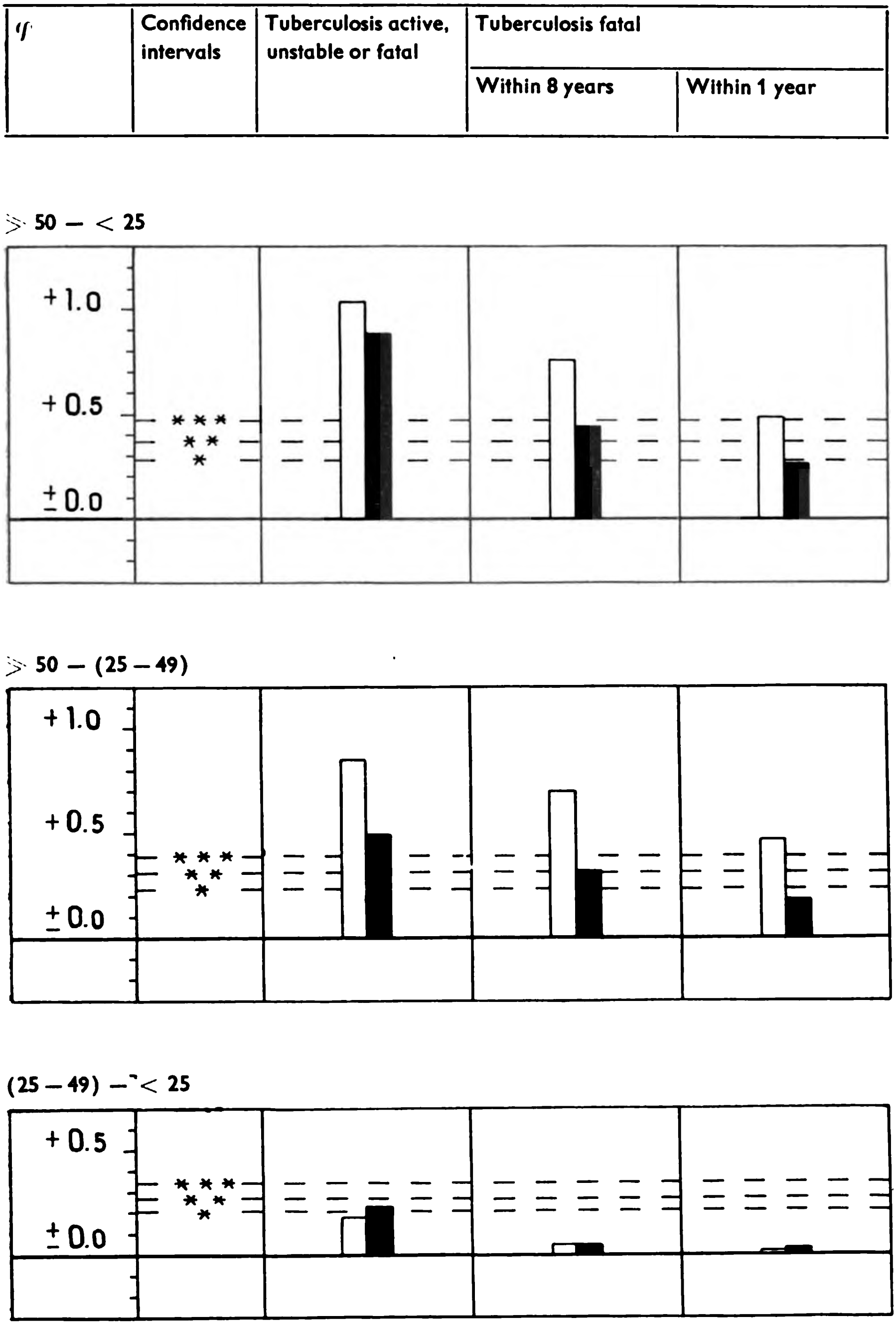
Age	No. of cases	Clinical material		Roentgenographic group			E. S. R.			
		Mass survey	Controls	Minimal	Mod. adv.	Far adv.	Non-pathologic	Elevated	Highly elevated	Not measured
< 25	145	56	89	74	34	37	61	53	30	1
		38.6	**61.4**	**51.0**	**23.4**	**25.5**	**42.1**	**36.6**	**20.7**	**0.7**
25—49 . . .	290	190	100	105	124	61	159	79	44	8
		65.5	**34.5**	**36.2**	**42.8**	**21.0**	**54.8**	**27.2**	**15.2**	**2.8**
≥ 50	113	68	45	14	47	52	23	45	32	13
		60.2	**39.8**	**12.4**	**41.6**	**46.0**	**20.4**	**39.8**	**28.3**	**11.5**
Total	548	314	234	193	205	150	243	177	106	22
		57.3	**42.7**	**35.2**	**37.4**	**27.4**	**44.3**	**32.3**	**19.3**	**4.0**

Conclusion: In homogenized material the prognosis in far advanced tuberculosis was considerably poorer in all respects as compared with the other roentgenographic groups. Moderately advanced tuberculosis differed from minimal disease mainly as regards total unfavourable prognosis, but also showed higher eight year mortality; the difference in first year mortality was not significant.

E.S.R. The diagram to tables 38 *a* and *b* illustrates the prognostic differences between the 3 E.S.R. groups.

In the heterogeneous material highly elevated E.S.R. was associated with much graver prognosis in all respects as compared with nonpathologic

Diagram to Tables 39 a and b. *Differences Between Various Age Groups in Heterogeneous* ☐ *and Homogenized* ■ *Material*



E.S.R. The differences were rather less between highly elevated and elevated readings and were considerably less between elevated and nonpathologic values. All the differences were highly significant.

After homogenization the differences between the highest E.S.R. group and the others were still great, but were less than in the heterogenous material. They were fairly similar as regards total unfavourable prognosis and first year mortality and most pronounced for eight year mortality. All were highly significant. In the comparison between elevated and nonpathologic E.S.R. the differences were still more reduced as compared with the heterogeneous material. Eight year mortality continued to show the greatest difference (almost significant), while total unfavourable prognosis and first year mortality displayed only tendencies in favour of the patients with nonpathologic E.S.R.

Conclusion: In homogenized material E.S.R. over 40 mm entailed considerably graver prognosis than did lower E.S.R. readings. The difference was greatest as regards eight year mortality. On the other hand, E.S.R. between borderline values and 40 mm as compared with nonpathologic E.S.R. involved only an almost significant difference in eight year mortality and in other prognostic respects tendencies without significance in favour of nonpathologic readings.

The few cases (4 per cent) in which the E.S.R. was not measured at diagnosis were not included in these calculations. As table 38 *a* shows, most of them had a fatal outcome.

Age: The diagram to tables 39 *a* and *b* illustrates the prognostic differences between the 3 age groups.

In the heterogeneous material the patients aged 50 years or more had a very much poorer total unfavourable prognosis than patients younger than 25 years; their disadvantage was somewhat less concerning eight year mortality and considerably less as regards first year mortality. All 3 differences were highly significant. Between the age groups 50 or over and 25 to 49, the differences in mortality remained almost unchanged, but that in total unfavourable prognosis was somewhat reduced. In this comparison, too, all differences were highly significant. The 25 to 49 and the younger than 25 age groups showed virtually no difference as regards mortality and only a tendency to lower frequency of total unfavourable prognosis in the latter group.

After homogenization practically all of these differences were reduced. The total unfavourable prognosis still was much higher in the patients aged 50 or over than in the group younger than 25. Highly significant differences were present between the former patients and each of the 2 younger groups as regards total unfavourable prognosis, significant differences in

eight year mortality, but only nonsignificant differences in first year mortality. Between the 25 to 49 group and the under 25 group there was a relatively small (almost significant) difference in total unfavourable prognosis, to the advantage of the younger group, and negligible difference concerning mortality.

Conclusion: The importance of age as a prognostic factor in homogenized material was rather less than that of roentgenographic status or of E.S.R. First year mortality showed only tendencies to higher frequency in patients aged 50 years or over than in younger patients. The eight year mortality was significantly higher in this oldest group than in the younger groups. The total unfavourable prognosis increased with age, but the difference was greater between patients aged 50 or over and those from 25 to 49 years old than between the latter group and patients younger than 25.

Comparison between control cases and survey-detected cases without and with homogenization for the prognostic factors

In heterogeneous and in homogenized material comparisons were made between the control cases and the survey cases, based on the complete series and on their component roengenographic groups. In the following presentation each comparison is illustrated by 2 tables and a diagram. The functions of the tables are the same as in the analysis of prognostic factors. The diagrams present the differences between heterogenous and between homogenized material.

The prognostic differences between *all control cases and all survey cases* are illustrated in the diagram to tables 40 *a* and *b*.

In the heterogeneous material the difference was greatest in regard to first year mortality, with poorer prognosis in the control cases. The preponderance of controls was somewhat less in the eight year mortality and was relatively small in the total unfavourable prognosis. The differences in eight year and first year mortality were highly significant and that concerning total unfavourable prognosis was significant.

After homogenization the differences diminished considerably in all 3 prognostic respects. The control cases, however, still showed significantly higher first year mortality, but otherwise only tendencies to poorer prognosis.

The results of the comparison between the *far advanced* cases in either series are presented in the diagram to tables 41 *a* and *b*.

In the heterogeneous material the differences in mortality between the far advanced groups were similar to those between the complete series.

As regards total unfavourable prognosis, however, there was a tendency to better results in the control cases. The difference in first year mortality was significant and that in eight year mortality was almost significant. Concerning total unfavourable prognosis the difference was not significant.

After homogenization the differences in mortality were relatively little reduced and that in total unfavourable prognosis increased slightly. The higher first year mortality among the controls was almost significant, but the difference in eight year mortality was not significant. The controls still showed a nonsignificant tendency to lower frequency of total unfavourable prognosis.

Because the far advanced cases constituted a minor proportion of the total material, the confidence intervals in the comparison of far advanced cases were considerably greater than for the total material.

The results of the comparison between the *moderately advanced* cases in either series are presented in the diagram to tables 42 *a* and *b*.

In the heterogeneous material the difference as regards first year mortality was fairly high, to the detriment of the control cases. Eight year mortality showed almost no difference and the total unfavourable prognosis was slightly greater in the controls than in the survey cases. The difference in first year mortality was almost significant.

After homogenization the difference in first year mortality was less but there was still a marked tendency to higher frequency in the controls. Eight year mortality still showed a negligible difference. Concerning total unfavourable prognosis, however, the difference was greater than in the heterogeneous material and was almost significant.

Because of the relatively small number of mass survey cases with far advanced tuberculosis, comparison was also made between *far advanced plus moderately advanced* cases in either series. This gave a wider basis for calculating differences. The results are shown in the diagram to tables 43 *a* and *b*.

In the heterogeneous material the differences strongly resembled those found between the totals of the 2 series. The control cases' greater frequency of first year and eight year mortality was highly significant and their preponderance in the total unfavourable prognosis was almost significant.

After homogenization these differences decreased approximately as in the comparison of the total series. First year mortality, however, showed a slightly greater difference here than between the total series. Apart from this difference, which was significant and implied higher frequency in the control cases, there were only minor tendencies in the same direction.

Comment on first year mortality. As earlier mentioned, these statistical calculations excluded the patients who died of other causes than pulmonary

TABLE 40 a. *Unfavourable Status at End of 8-Year Follow-up of All Roentgenographic Groups of Active Pulmonary Tuberculosis in Mass Survey Cases and in Controls. Heterogeneous Material (cf. table 40 b and diagram)*

All roentgenographic groups	No. of cases	Unfavourable results at end of 8 years					
		Tuberculosis active, unstable or fatal		Tuberculosis fatal			
				Within 8 years		Within 1 year	
		No.	%	*No.*	%	*No.*	%
Mass survey	314	115	36.6	41	13.1	13	4.1
Controls . .	234	117	50.0	73	31.2	53	22.6
Total	548	232	42.3	114	20.8	66	12.0

Diagram to Tables 40 a and b. *Differences Between All Control Cases and All Mass Survey Cases in Heterogeneous □ and Homogenized ■ Material*

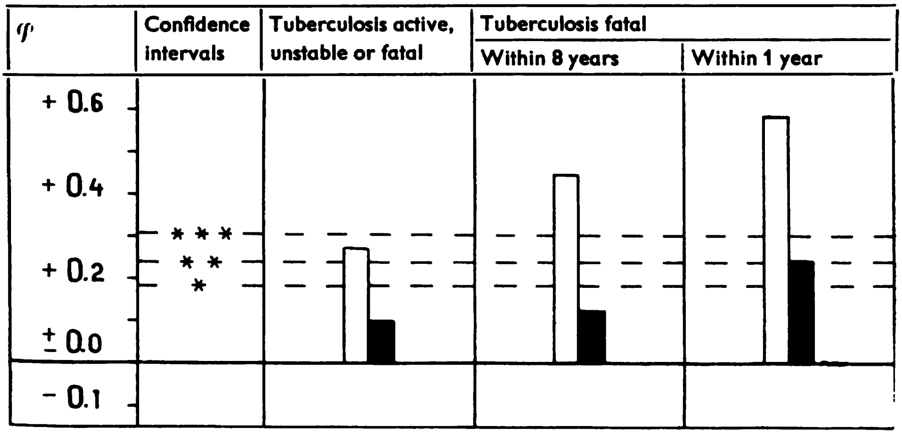


TABLE 40 b. *Roentgenographic Extent of Disease, E. S. R. and Age at Diagnosis in All Mass Survey Cases and All Controls (relationship in %)*

All roentgenographic groups	No. of cases	Roentgenographic group			E. S. R.				Age		
		Minimal	Mod. adv.	Far adv.	Non-pathologic	Elevated	Highly elevated	Not measured	< 25	25—49	≥ 50
Mass survey	314	130 **41.4**	130 **41.4**	54 **17.2**	177 **56.4**	95 **30.3**	29 **9.2**	13 **4.1**	56 **17.8**	190 **60.5**	68 **21.7**
Controls . .	234	63 **26.9**	75 **32.1**	96 **41.0**	66 **28.2**	82 **35.0**	77 **32.9**	9 **3.8**	89 **38.0**	100 **42.7**	45 **19.2**
Total	548	193 **35.2**	205 **37.4**	150 **27.4**	243 **44.3**	177 **32.3**	106 **19.3**	22 **4.0**	145 **26.5**	290 **52.9**	113 **20.6**

Table 41 a. *Unfavourable Status at End of 8-Year Follow-up of Far Advanced Active Pulmonary Tuberculosis in Mass Survey Cases and in Controls. Heterogeneous Material (cf. table 41 b and diagram)*

Far advanced tuberculosis	No. of cases	Unfavourable results at end of 8 years					
		Tuberculosis active, unstable or fatal		Tuberculosis fatal			
				Within 8 years		Within 1 year	
		No.	%	*No.*	%	*No.*	%
Mass survey	54	43	79.6	24	44.4	11	20.4
Controls . .	96	72	75.0	62	64.6	45	46.9
Total	150	115	76.7	86	57.3	56	37.3

Diagram to Tables 41 a and b. *Differences Between Far Advanced Control Cases and Far Advanced Mass Survey Cases in Heterogeneous ☐ and Homogenized ■ Material*

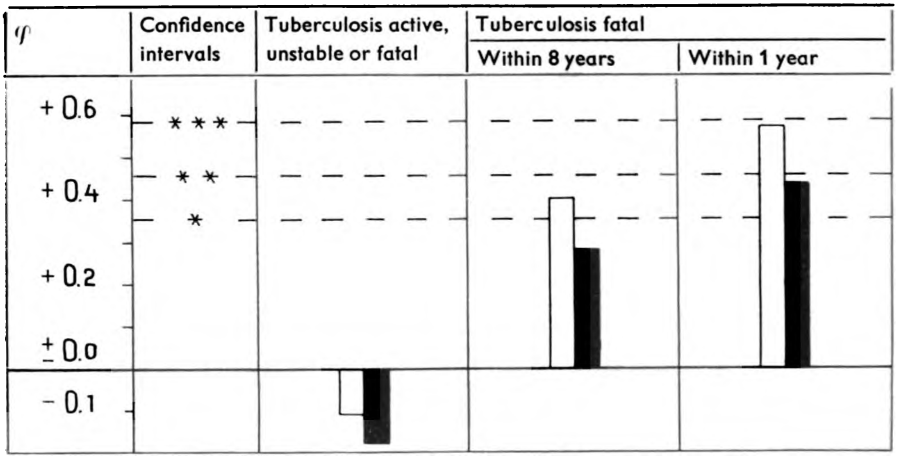


Table 41 b. *E. S. R. and Age at Diagnosis in Far Advanced Mass Survey and Control Cases (relationship in %)*

Far advanced tuberculosis	No. of cases	E. S. R.				Age		
		Non-pathologic	Elevated	Highly elevated	Not measured	< 25	25—49	⩾ 50
Mass survey	54	7	28	13	6	10	24	20
		13.0	**51.9**	**24.1**	**11.1**	**18.5**	**44.4**	**37.0**
Controls	96	7	31	50	8	27	37	32
		7.3	**32.3**	**52.1**	**8.3**	**28.1**	**38.5**	**33.3**
Total	150	14	59	63	14	37	61	52
		9.3	**39.3**	**42.0**	**9.3**	**24.7**	**40.7**	**34.7**

Table 42 a. *Unfavourable Status at End of 8-Year Follow-up of Moderately Advanced Active Pulmonary Tuberculosis in Mass Survey Cases and in Controls. Heterogeneous Material (cf. table 42 b and diagram)*

Moderately advanced tuberculosis	No. of cases	Unfavourable results at end of 8 years					
		Tuberculosis active, unstable or fatal		Tuberculosis fatal			
				Within 8 years		Within 1 year	
		No.	%	*No.*	%	*No.*	%
Mass survey	130	47	36.2	14	10.8	2	1.5
Controls . .	75	33	44.0	9	12.0	7	9.3
Total	205	80	39.0	23	11.2	9	4.4

Diagram to Tables 42 a and b. *Differences Between Moderately Advanced Control Cases and Moderately Advanced Mass Survey Cases in Heterogeneous* ☐ *and Homogenized* ■ *Material*

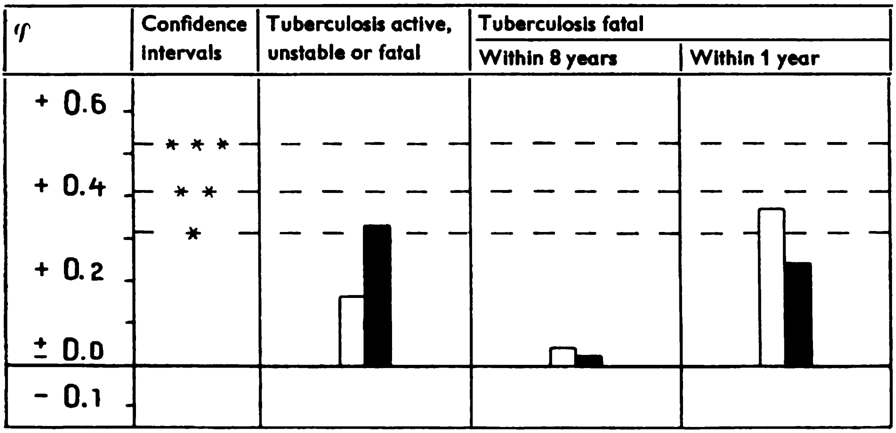


Table 42 b. *E. S. R. and Age at Diagnosis in Moderately Advanced Mass Survey and Control Cases (relationship in %)*

Moderately advanced tuberculosis	No. of cases	E. S. R.				Age		
		Non-pathologic	Elevated	Highly elevated	Not measured	< 25	25—49	> 50
Mass survey	130	75	39	11	5	10	86	34
		57.7	**30.0**	**8.5**	**3.8**	**7.7**	**66.2**	**26.2**
Controls	75	26	31	17	1	24	38	13
		34.7	**41.3**	**22.7**	**1.3**	**32.0**	**50.7**	**17.3**
Total	205	101	70	28	6	34	124	47
		49.3	**34.1**	**13.7**	**2.9**	**16.6**	**60.5**	**22.9**

TABLE 43 a. *Unfavourable Status at End of 8-Year Follow-up of Far and Moderately Advanced Active Pulmonary Tuberculosis in Mass Survey Cases and in Controls. Heterogeneous Material (cf. table 43 b and diagram)*

Far and moderately advanced tuberculosis	No. of cases	Unfavourable results at end of 8 years					
		Tuberculosis active, unstable or fatal		Tuberculosis fatal			
				Within 8 years		Within 1 year	
		No.	%	*No.*	%	*No.*	%
Mass survey	184	90	48.9	38	20.7	13	7.1
Controls . .	171	105	61.4	71	41.5	52	30.4
Total	355	195	54.9	109	30.7	65	18.3

Diagram to Tables 43 a and b. *Differences Between Far plus Moderately Advanced Control Cases and Far plus Moderately Advanced Mass Survey Cases in Heterogeneous* ☐ *and Homogenized* ■ *Material*

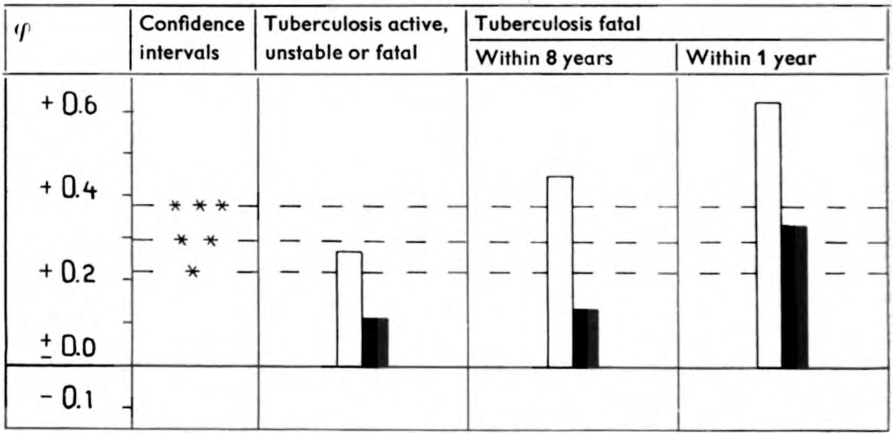


TABLE 43 b. *E. S. R. and Age at Diagnosis in Far and Moderately Advanced Mass Survey and Control Cases (relationship in %)*

Far and moderately advanced tuberculosis	No. of cases	E. S. R.				Age		
		Non-pathologic	Elevated	Highly elevated	Not measured	< 25	25—49	≥ 50
Mass survey	184	82	67	24	11	20	110	54
		44.6	**36.4**	**13.0**	**6.0**	**10.9**	**59.8**	**29.3**
Controls	171	33	62	67	9	51	75	45
		19.3	**36.3**	**39.2**	**5.3**	**29.8**	**43.9**	**26.3**
Total	355	115	129	91	20	71	185	99
		32.4	**36.3**	**25.6**	**5.6**	**20.0**	**52.1**	**27.9**

tuberculosis (c. 5 per cent of the survey series and of the controls), the 2 emigrants and the 5 patients not examined at the end of 8 years. Concerning first year mortality, however, tests were made with inclusion in the homogenized material of such of those persons as were still alive one year after diagnosis. The difference in favour of the survey cases was thereby accentuated. Between the far advanced groups the difference in first year mortality increased from almost significant to significant. Other significances in the differences between controls and survey cases were unaltered. Corresponding tests were made with the principal prognostic factors, but produced no changes in significance.

Comment on differences. In moderately advanced tuberculosis there was a relatively large difference (almost significant) involving total unfavourable prognosis, with poorer results among the control cases. The reason for this difference is obscure. No direct explanation emerged from study of the basic data. However, since the differences in total unfavorable prognosis between control cases and survey cases in the various roentgenographic groups lacked uniformity of direction, it is most probable that the relevant difference between the moderately advanced cases was attributable to chance.

It was not surprising that the greatest prognostic difference should occur in the far advanced cases. By definition such cases may even to-day range from the therapeutically accessible to the untreatable moribund. At the time from which my cases were collected, extrathoracic spread of tuberculosis, which was most common in the far advanced control group, generally was a terminal occurrence, as specific antimicrobial agents were still scarce.

Conclusion: In the homogenized material the control cases thus showed significantly higher first year mortality than the survey cases, and this difference was mainly attributable to the far advanced cases. In the other prognostic respects there were no significant differences between the totals of the survey series and the control series.

Table 44 presents a *survey of the significant differences* found between the various groups of the prognostic factors and also between the control cases and the cases detected by mass radiography.

2. *Tuberculosis without demonstrated activity initially or later*

In mass radiography and also in routine antituberculois work the fact that the activity of pulmonary lesions cannot in all cases be determined at diagnosis results in a number of persons being placed under supervision for lesions which continued observation shows to have lacked activity.

TABLE 44. *The Importance of Some Prognostic Factors and of Method of Diagnosis in Homogenized Groups*
Asterisks Denote Degree of Significance of the Differences Between Groups

Prognostic factors	Comparisons between	Significance of differences between groups with reference to unfavourable results at end of 8 years		
		Tuberculosis active, unstable or fatal	Tuberculosis fatal	
			within 8 years	within 1 year
Roentgeno-graphic extent at diagnosis	Far adv. — Minimal	***	***	***
	Far adv. — Mod. adv.	***	***	***
	Mod. adv. — Minimal	**	*	
E. S. R. at diagnosis	Highly elevated — nonpathologic	***	***	***
	Highly elevated — elevated	***	***	***
	Elevated — nonpatho-logic		*	
Age at diagnosis	≥ 50 — < 25	***	**	
	≥ 50 — (25—49)	***	**	
	(25—49) — < 25	*		
	Controls — mass survey			**

*** = highly significant ** = significant * = almost significant

After all the data in a case have been collected over a period of years it is, of course, easier to assess this initial activity in retrospect. Even this method, however, does not always yield a decisive answer and the difficulties increase with the strictness of the criteria for inactivity.

Tuberculosis of doubtful or no activity was, for obvious reasons, more common in the cases diagnosed by mass radiography than in the control series. Lack of antecedent roentgenograms for comparison with many of the positive survey films, this being the first county-wide radiographic survey of Södermanland, was an important contributory cause of this difference between the two series.

The cases in which tuberculosis was not active at diagnosis but became active later are separately described (p. 124). Those without demonstrated activity initially or later are briefly reported in the following pages.

I *Probably active:* In these cases the tuberculous lesions were suspected to be active at diagnosis, but activity could not be proved then or during the observation period. The category was relatively small, comprising 5.2 per cent of all the registered mass survey series and 1.4 per cent of the total control material. Of the 35 patients with probably active tuberculosis in the mass survey group, 18 were men and 17 women and the corresponding figures in the control series were 4, 2 and 2.

The following figures summarize the results in these cases after 8 years of observation.

	No. diagnosed	Died during observation period	Still registered 8 years after diagnosis
Mass survey cases	35	13	11
Control cases	4	2	2

Of the 11 mass survey cases still on the tuberculosis register, 4 were old people who were unfit to attend regularly for examination. One of them also had diabetes. Of the 7 younger patients, 1 refused supervision and in the others there were special reasons for careful observation, such as coexistent nontuberculous disease or tuberculosis in contacts. One of the 2 remaining controls was elderly and had complicating bronchiectasis and the other, whose history included pleurisy, was released from observation in the ninth year.

II *Inactive:* The criteria for inactivity were stated on page 29. Briefly, they were that the lesions should appear roentgenographically healed and stable for at least 5 years. If the observation period was shorter, "manifest healing" should be evident on roentgenograms or at autopsy. There were 142 cases of inactive tuberculosis in the mass survey series of registered tuberculosis (21.0 per cent) and 14 in the control material (4.8 per cent). The former group consisted of 71 males and 71 females and the latter of 5 males and 9 females.

The results in the inactive cases 8 years after diagnosis were as follows.

	No. diagnosed	Died during observation period	Still registered 8 years after diagnosis
Mass survey cases	142	6	8
Control cases	14		1

Of the 8 mass survey cases remaining on the tuberculosis register, 1 was released from supervision in the following year. In 2 of the others the relatively long observation period despite unaltered roentgenographic findings was explained by coexistent nontuberculous disease, and in 5 by senile infirmity preventing regular examination. In the remaining control

case the records showed a history of pleurisy and familial tuberculosis; this case was deleted from the register in the ninth year.

III *Probably inactive:* The roentgenographic appearance of the tuberculous lesions was stable but retrospective assessment failed to show convincing healing at the time of diagnosis, or the observation period was too short for classification as inactive. Of the registered mass survey cases, 111 (16.4 per cent) and of the controls 21 (7.2 per cent) were judged to have had probably inactive tuberculosis at diagnosis. Males numbered 59 and females 52 in the mass survey group and the corresponding figures in the controls were 13 and 8.

The fate of these patients at the end of 8 years is indicated by the following data.

	No. diagnosed	Died during observation period	Still registered 8 years after diagnosis
Mass survey cases	111	33	41
Control cases	21	7	3

Sixteen of the 41 mass survey cases remaining on the tuberculosis register were old persons who were too infirm for regular examination and/or also had other pulmonary lesions such as bronchiectasis. Three of the younger patients refused regular examination. The professions of 5 others (food handling, teaching, etc.) demanded special watchfulness as regards tuberculosis. Two patients were mentally ill and 1 was mentally deficient. In almost all of the remaining 14 cases there were special reasons for close observation (e.g., strong tuberculous heredity, coexistence of other structural changes in the lungs, or active tuberculosis in contacts). Two of these patients were freed from supervision in the ninth year after diagnosis and 3 in the tenth year. Of the 3 control patients who were still registered after 8 years, 1 was almost 80 years old and housebound and 2 were released from observation in the ninth year.

The mortality in the probably inactive cases may seem high in comparison with that among the definitely inactive cases. By curtailing the period of observation, however, death from nontuberculous disease frequently prevented classification as definitely inactive tuberculosis.

3. *Tuberculosis initially not active, later active*

Among the cases of tuberculosis which retrospective review showed not to have been active at diagnosis, one category invited special interest. It comprised cases in which the late occurrence of demonstrable tubercu-

TABLE 45. *Age at Diagnosis in Cases with "Later Activity"*

Initial status (modified NTA classification)	Age at diagnosis 15—24	25—34	35—49	50—69	>70 years	Total
	Mass survey					
Minimal I	1	4	8	2	1	16
Minimal II		3	3	3		9
Moderately advanced		4	9	6	1	20
Far advanced				2	2	4
Total	1	11	20	13	4	49
	Controls					
Minimal I		1		2		3
Minimal II			1			1
Moderately advanced				1		1
Total		1	1	3		5

lous activity, together with other findings, excluded definite activity at diagnosis.

The mass radiographic survey revealed 49 cases of this type (7.2 per cent of all registered cases) and the control series contained 5 cases (1.5 per cent). The male:female ratio was 33:16 in the mass survey cases and 1:4 in the controls.

In table 45 the cases with later activity are grouped according to age and extent of tuberculosis at diagnosis (modified NTA classification). The largest age group was 35 to 49 years.

The retrospective evaluation of activity at diagnosis and the interval from diagnosis to first signs of definite activity are seen in table 46. In all cases but 2 this first evidence of progression was roentgenographic; in the 2 exceptions positive bacteriologic findings preceded roentgenographic change. Definitely inactive tuberculosis at diagnosis was comparatively rare in the cases with later activity in the mass survey group and was absent in the control group. Probably active at diagnosis were 27 cases and probably inactive were 17 of the 49 in the mass survey group. The small total (5) of the control cases did not permit conclusions in this or other respects. In 4 of these 5, however, the interval to activity was as long as 5 to 7 years.

Progression occurred as exudative pleurisy in 2 of the mass survey series and in 1 of the controls. In another mass survey case tuberculous empyema developed in an old, persistent pneumothorax space. In a

TABLE 46. *Cases with "Later Activity": Initial Status and Interval Between Diagnosis and Signs of Activity*

Initial activity of lesions	Modified NTA classification	Interval from diagnosis to definite activity							Total
		1—2	2—3	3—4	4—5	5—6	6—7	7—8 years	
		Mass survey							
Probably active . . .	Minimal I			2	2	2	3		9
	Minimal II	2	1			2			5
	Moderately advanced	2	2	2			2	1	9
	Far advanced	1			3				4
Probably inactive . . .	Minimal I				1		2	1	4
	Minimal II		1	1				1	3
	Moderately advanced	1	2		2	2	2	1	10
Inactive . . .	Minimal I				1			2	3
	Minimal II			1					1
	Moderately advanced		1						1
	Total	6	7	6	9	6	9	6	49
		Controls							
Probably active . . .	Minimal I					1			1
	Minimal II						1		1
	Moderately advanced					1			1
Probably inactive . . .	Minimal I		1				1		2
	Total		1			2	2		5

fourth mass survey case exudative pleurisy accompanied progression of the pulmonary lesions.

As regards the extent of the tuberculosis at diagnosis, half of the mass survey cases and 4 of the 5 controls had minimal lesions. Only 4 persons had far advanced lesions, all of them retrospectively classed as probably active on films from the mass survey.

The interval from diagnosis to demonstrated tuberculous activity was fairly evenly distributed, with 6 to 9 cases per year. Of the 49 mass survey cases, 6 had been removed from the tuberculosis register as cured for periods ranging from 1 to 5 years before progression was detected.

The course of tuberculosis in some of these "later active" cases was grave. Thus, artificial pneumothorax was given in 4 mass survey cases and 2 others of the same group underwent lobectomy. Three persons from the mass survey group died of pulmonary tuberculosis. One of these, a

77-year-old man whose diagnostic films were retrospectively interpreted as showing probably inactive tuberculosis, developed acute spread of the disease about 2 years later and tubercle bacilli were found on direct microscopy of sputum; he died shortly afterwards. The second fatal case was a 56-year-old woman who had probably active tuberculosis at diagnosis and died in the seventh year of observation; she also had severe chronic polyarthritis. The third patient, an 83-year-old man, likewise had probably active tuberculosis at diagnosis and died in the seventh year of observation.

4. *Discussion*

Tuberculosis active at diagnosis

In the follow-up investigation most interest naturally was attached to the patients whose tuberculosis was active at diagnosis. The prognostic comparison between active cases detected by mass radiography and those diagnosed by other means was based on the changes which took place during an observation period of 8 to 10 years. For some purposes I found it appropriate to classify the cases according to roentgenographic extent of tuberculosis at diagnosis, using the three NTA groups (minimal, moderately advanced and far advanced) with or without modification. Such classification was used for studying roentgenographic progression and regression, deaths from tuberculosis and type and frequency of active therapy and also in the statistical analysis of prognosis. On the other hand, study of bacteriologic findings during the follow-up period, hospitalization and specific medication, and clinical evaluation of final status were, for various reasons, performed with the survey series and the control series undivided.

Cavitary roentgenographic *progression* occurred in all NTA groups. Of the cases with minimal tuberculosis at diagnosis, c. 17 per cent in the survey series and c. 11 per cent in the control series developed excavation. The mildest of all the groups (minimal I) showed similar frequencies. These figures illustrate the necessity of adequate supervision even in minimal tuberculosis. Within the various roentgenographic groups the annual frequencies of roentgenographic progression and regression were highly similar. An exception, however, was progression during the first year of observation in far advanced tuberculosis; this was significantly more common in the control group than in the group from the mass survey. The difference was also reflected in the *mortality* from pulmonary tuberculosis among the total cases, which during the first year was 21.4 per cent in the control series but

only 3.8 per cent in the survey series, the discrepancy being mainly attributable to the far advanced cases. For the whole 8-year period the tuberculosis mortality was 29.4 per cent in the control series and 12.1 per cent in the cases detected by mass survey.

The higher total of positive *bacteriologic findings* among the controls as compared with the survey cases must be attributed to the higher proportion of patients with advanced tuberculosis in the former group.

Concerning the most widely used form of therapy, *sanatorium care*, *Fraser* (1951), whose study comprised only hospitalized cases, stated that those discovered by mass radiography required on average 1 month longer hospital stay than did his controls. His calculations were based on nonfatal cases. By contrast, he pointed out *Kerley's* (1950) statement that 332 cases of active, mass-survey detected tuberculosis required a mean of 6 to 7 months in hospital as against 18 months for comparable control cases. *Fraser* ascribed the somewhat longer hospitalization in his survey cases to their greater suitability for therapeutic measures. *Anderson, Enterline, Hill & Roberts* (1954) wrote that early discovery of tuberculosis by mass radiography might be expected to result in saving in hospital care. They found, however, that during a 4-year follow-up period 81 per cent of their survey-detected cases and 84 per cent of their nonsurvey group were hospitalized. Of these hospitalized cases, 10 per cent of the survey group but only 5 per cent of the control group returned for further hospital care. Consequently, the total duration of hospitalization was greater in the survey series. The explanation offered by *Anderson et al.* was the higher mortality (from all causes) in their controls — 45.7 per cent as compared with 13.4 per cent among the survey group. They estimated that, with the same mortality, the survey-discovered cases would actually have required less hospitalization than the controls.

In my investigation 71.4 per cent of the active cases from the mass survey and 86.7 per cent of the active control cases were hospitalized at some time during the observation period. Of the hospitalized survey cases 38.0 per cent were readmitted and the corresponding frequency in the control series was 37.2 per cent. In contrast to *Anderson et al.*, therefore, I found no difference in the percentage of rehospitalized cases. Despite higher mortality during the first year of follow-up, hospitalization in the control series not only was somewhat more frequent, but also tended to be longer than in the survey series.

The frequency of hospitalization and of bacteriologic studies was so high that distribution according to roentgenographic status could not be expected to contribute anything further of value for the investigation.

The introduction of *specific drugs* against tuberculosis coincided approximately with the period from which the first of my cases were collected.

Because of the great initial scarcity of such drugs, they were given during the first year after diagnosis to only slightly more than 3 per cent of the combined mass survey and control series. As specific medication gradually became available for all cases in which it was indicated, about 35 per cent of both series were so treated at some time during the follow-up period. The paucity of cases given the early, decisive medication, however, meant that if the series were divided in this respect into roentgenographic groups, these would be very small. Consequently, the series were studied undivided as regards specific medication. With present knowledge of the potency of such drugs, the only reasonably permissible inference from the slightly higher frequency of specific medication in the control series than in the survey group is that the considerably poorer prognosis in the former cases was thereby insignificantly improved.

Artificial pneumothorax was subjected to detailed analysis as being the most widely used active treatment during the time in question. Since the indications for pneumothorax were largely determined by the extent of the pulmonary tuberculosis, the frequency of this treatment was studied with the cases distributed into 6 roentgenographic groups. The cavitary cases of moderately advanced tuberculosis showed the highest frequency of pneumothorax — about 60 per cent in both the survey series and the control series. Otherwise the control cases received rather more pneumothorax treatment than did the survey-detected cases. Satisfactory collapse according to the definition used, however, was more common in the survey series. The evidence from the investigation was that the rules for using artificial pneumothorax were alike in the survey series and in the controls, and that the patients received this treatment to the extent that it was warranted by their condition.

Thoracoplasty was relatively seldom performed in this case material and *pulmonary resection* was rare.

The *analysis of therapy* thus showed that the mass survey cases and the controls on the whole received similar treatment on uniform indications. A slight preponderance in the frequency of therapy was discernible in the control series, however, and this is important, since it implies that the poorer prognosis in that series was scarcely attributable to lack of therapy as compared with the survey-detected cases.

As already stated, *prognosis* was assessed after 8 to 10 years of observation. Since in all cases at least 8 years elapsed between diagnosis and prognostic assessment, the results after 8 years were attributed most importance. In the *clinical evaluation* of active cases the total survey series was found to have better prognosis than the total controls. The difference as regards medical results was statistically significant and that from the economic aspect (fitness for work) was highly significant. Patients who died from

other causes than pulmonary tuberculosis (about 5 per cent of both series) were excluded from these calculations.

Since all registrations of pulmonary tuberculosis were made by the same physicians and according to the same principles, it might have been considered warrantable to compare prognosis in *all* registered survey cases with that in *all* control cases, without regard to the retrospective evaluation of activity. The better outlook for mass-survey detected tuberculosis would then have been further accentuated. Such comparison, however, would have been unsatisfactory, as lesions which subsequently are shown to have lacked activity inevitably are more commonly detected and registered as the result of mass radiography than in routine antituberculosis work.

It would have been of interest to compare my findings with those from other prognostic studies of mass-survey detected tuberculosis. Truly comparable material seems to be very difficult to obtain, however. The discrepancies may involve age, sex, race, or other population factors, activity of the lesions, or low participation rate in the mass survey examination and at follow-up. The series with controls presented in table 2 show such inconsistencies with each other and with my cases as to preclude detailed comparisons. The only permissible conclusion is that the prognosis was invariably better in series of tuberculosis cases detected by mass radiography than in control material.

Between mass-survey detected cases of pulmonary tuberculosis and control cases diagnosed at the same time in the same population, the main difference, of course is associated with the fact that in the former cases the lesions are revealed earlier than would have occurred with routine antituberculosis control. One might anticipate that two cases diagnosed in the same roentgenographic stage of tuberculosis would have the same prognosis, but this is not necessarily so, since other factors than roentgenographic status are also important for prognosis. Moreover, the usual NTA classification, or even fairly detailed subdivisions of it, allow variations within the group or subgroup boundaries.

The *statistical analysis* showed that in my case material the factors of greatest importance for prognosis were the roentgenographic extent of tuberculosis, the E.S.R. and age at diagnosis. Treatment, of course, also influenced the prognosis. But in a chronic, commonly relapsing disease such as pulmonary tuberculosis, treatment as a factor is difficult to isolate after a long period of observation. One reason is that treatment may have been given initially or later, depending on progression of the lesions or on therapeutic advances. Since I found that the survey series and the control series were treated to the same extent and with the same methods, I did not consider it necessary to test treatment as a possible prognostic factor in the homogenization procedure.

The influence of the principal prognostic factors was illustrated by comparisons between homogenized groups of combined mass survey and control cases. The control cases and the survey cases were then compared as regards results after 8 years.

The basis for the comparisons was unfavourable prognosis. This was studied from three aspects, viz., death from pulmonary tuberculosis within 1 year of diagnosis, death within 8 years and total of morbidity and mortality from tuberculosis at the end of 8 years.

The only significant difference between the homogenized control series and the homogenized survey series was a higher mortality rate during the first year in the controls. In practically all comparisons with homogenized material, however, there was a tendency to poorer prognosis in the control cases.

In fully homogenized material the method of diagnosis should not as such have given rise to any prognostic differences. Those that appeared must be regarded as chiefly dependent on the variations which, despite the homogenization used, occurred within each roentgenographic group. Such variations mainly involved the extent of the lesions, but also concerned E.S.R. and age, even after the values of these factors were divided into groups.

The fact that, apart from the significant difference in first-year mortality (which was easily explained by variations within the far advanced group), only tendencies to prognostic difference were found between the totals of the homogenized series, indicates uniformity, independent of the method of diagnosis, in the retrospective clinical review.

Tuberculosis without demonstrated activity initially or later

As regards follow-up, the only real interest of these cases in implied in the definition, i. e., that neither at diagnosis nor throughout the observation period did they show signs of active tuberculosis. They nevertheless evoke some reflections. It was considered necessary to supervise them, since when the lesions were detected the question of activity could not be decided.

It was to be expected that tuberculosis of doubtful or no activity should be more common in elderly than in younger persons. Nor was it surprising that the number of such cases was high in my material, which derived from a total population of about 54,000 persons aged 50 years or over and about 147,000 younger than 50. In the former age group were 59 per cent of the persons without active tuberculosis in the mass survey series of registered cases and 51 per cent of the corresponding control cases.

The naturally higher death rate in the older age groups was particularly apparent in the *probably inactive* group and in the relatively small *probably active* group. About one-third of these patients died of nontuberculous causes during the observation period but many of them, had they survived for the stipulated observation period, would have been classifiable as *inactive*. In the inactive group, which was the largest of the three, the death rate was less than 4 per cent.

These groups without demonstrated tuberculous activity together comprised rather more than 40 per cent of the total mass survey series of registered cases and about 13 per cent of the total controls. The sex distribution, as in the total series, was equal. In considering the high proportion of survey cases without active tuberculosis, one must keep in mind that this was the first county-wide investigation of Södermanland. In the second survey (1953 to 1955), the corresponding figure fell to 25.2 per cent and, given the same period of observation as after the first survey, would probably have been even lower. An important reason for the reduction was that many "positive" films in the second survey could be classed as insignificant after comparison with survey and postsurvey films from 1946 to 1948.

The justification of supervising other cases than those with obviously active tuberculosis was demonstrated by the cases in which lesions without activity at diagnosis became active later.

Tuberculosis initially not active, later active

These "later active" cases underline the difficulties which may be encountered when the risk of relapse, and thereby the time for deletion from the tuberculosis register, is evaluated for individual patients. If the statutory 5 years without activity had always been directly followed by removal from the register, not a few patients would have been deprived of highly necessary observation.

The patients whose tuberculosis was, by retrospective evaluation, inactive or probably inactive at diagnosis, numbered 312 in the combined mass survey and control series. Of these, 24 showed signs of active tuberculosis during the 8-year observation period; in 12 of them activity first appeared after the end of the fifth year. The risk that the registered cases of inactive or probably inactive tuberculosis would become active at some time during 8 years therefore was at least 7.7 per cent, and the risk after 5 years was at least 3.8 per cent.

Risk of "missed" renotification after deregistration

The risk that tuberculous reactivation leading to reregistration would escape my knowledge was very small. Reregistrations within Södermanland County automatically became known. The frequency of migration from Södermanland to other counties was very low in the registered cases. During the whole of the observation period 60 of the mass survey series and 31 of the controls left Södermanland. In the survey series the annual rate of outward migration ranged from 0.9 to 2.1 per cent of those remaining on the register, and in the control series the corresponding range was 0.7 to 3.8 per cent.

Concerning all the patients who left Södermanland while still registered, information was obtained from the new place of residence. Only if a case was deleted from the register in that second county and then reregistered in a third could the relapse have remained unknown in Södermanland. Since, of the migrants from Södermanland, only 29 survey cases and 10 controls were removed from the register in another county, this latter contingency must have been extremely rare. The surest guarantee that reregistration outside of Södermanland did not evade my notice was the custom of requesting information of such cases from the tuberculosis dispensaries at which they previously were known. In Södermanland all such requests are filed in the case records.

CHAPTER X

COEXISTENT MENTAL ILLNESS OR DEFICIENCY AND PULMONARY TUBERCULOSIS

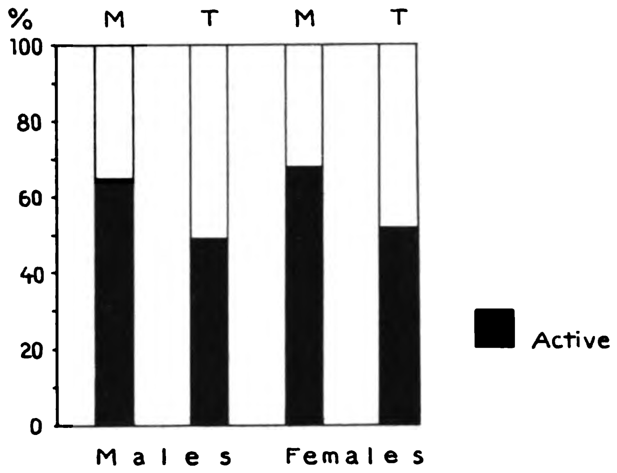
Ever since antiquity the possibility of a relationship between mental illness or deficiency and tuberculosis has been the subject of lively debate. The literature is much too extensive for review here, but it was exhaustively surveyed by *Grigg* (1955) who, in the introduction to his "Historical and bibliographical review of tuberculosis in the mentally ill", stated: "As of today the mental institution is one of the few remaining strongholds of tuberculosis, perhaps its last stand in civilized countries." This would seem also to express a general opinion that the frequency of tuberculosis is higher in such institutions than in the general population.

1. *Material and results*

When the mass radiographic survey of Södermanland County began in 1946, there were in the county 1,578 institutional beds for mentally ill and 559 for mentally deficient persons. Most of these persons participated in the mass survey and 56 were notified and registered as having pulmonary tuberculosis. The mass survey series of registered tuberculosis cases contained strikingly more mentally ill or deficient persons (8.3 per cent) than did the control series (2.7 per cent).

In my retrospective evaluation of the activity of tuberculosis at diagnosis, I found that of the patients with coexistent mental disorder in the mass survey series 20 of the 31 males and 17 of the 25 females were in the category *"initially active"*. All the 8 mentally disordered patients in the control material had active tuberculosis at diagnosis. The somewhat greater frequency of initially active tuberculosis in the mental patients from the mass survey series as compared with the total mass survey group is seen in figure 23. The difference, however, was not statistically significant for either sex.

The age distribution in the patients with coexistent mental disorder and active pulmonary tuberculosis was as follows.



M = mentally ill or deficient mass survey cases
T = total mass survey cases

Fig. 23. **Initial activity of tuberculosis in cases with coexistent mental disorder and in total mass survey cases.**

	7—14	*15—24*	*25—34*	*35—49*	*50—69*	≥ *70*	*Total*
Mass survey cases							
Males	1	1	4	8	6		20
Females		4	5	7	1		17
Total	*1*	*5*	*9*	*15*	*7*		*37*
Control cases							
Males				1	1		2
Females		1		3	1	1	6
Total		*1*		*4*	*2*	*1*	*8*

Far advanced tuberculosis was more common in the mentally ill or deficient patients than in the initially active cases of the mass survey series as a whole. For this difference, however, the female mental patients were alone responsible (fig. 24). Far advanced tuberculosis was present at diagnosis in 7 (41.2 per cent) of them and in 4 (20.0 per cent) of the males. The corresponding percentages for the complete mass-survey detected series of initially active tuberculosis were 14.9 and 19.3. Statistical analysis showed the difference in the female cases to be significant. The chi-square value was 8.1 $0.001 < P < 0.005$. The difference in the male cases was not significant.

Mortality from tuberculosis was greater (35.1 per cent, or 9 females and 4 males) in the patients with mental disorder and active tuberculosis

than in the total of initially active tuberculosis cases discovered by mass radiography (12.4 per cent). The difference in the male cases (20.0 *v.* 12.9 per cent) was not statistically significant, but that in the females (52.9 *v.* 11.9 per cent) was highly significant (26.2 $P < 0.001$). This finding tallies with the greater frequency of far advanced tuberculosis in the female mental patients. The mortality from tuberculosis is illustrated in figure 25.

In all of the 8 persons in the control series who had coexistent mental disorder and active pulmonary tuberculosis the latter disease was moderately or far advanced. Four of the 8 died of pulmonary tuberculosis.

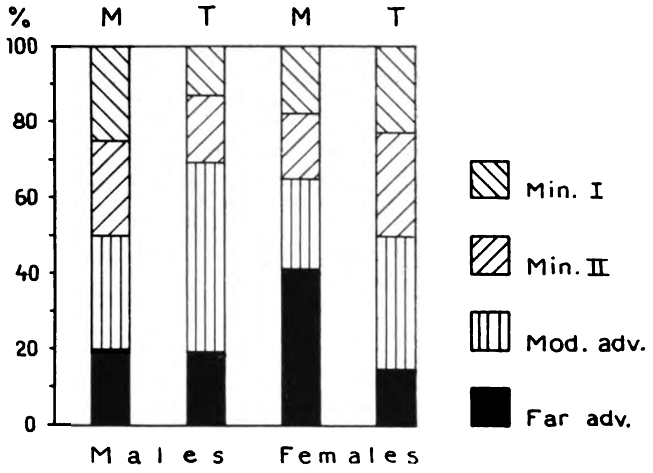
The presence of mental illness or deficiency renders active *therapy* for tuberculosis more difficult than in mentally healthy persons. No active anti-tuberculosis interventions were made in any mental patients in the mass survey group, and in only 2 of those in the control series was artificial pneumothorax induced. Specific medication, on the other hand, was given in 8 of the mass survey series and in 3 of the control cases.

2. *Discussion*

The large number of persons with mental illness or deficiency in whom pulmonary tuberculosis was not detected until mass radiography was undertaken demonstrated the need for routine anti-tuberculosis measures in mental institutions. The considerably higher mortality from tuberculosis among the mental patients in my series than among the mass survey series as a whole was shown to be associated with a preponderance of far advanced tuberculosis in the females. In the males, on the other hand, the extent of active tuberculosis was similar in the mentally disordered patients and in the total series, as also was mortality from tuberculosis.

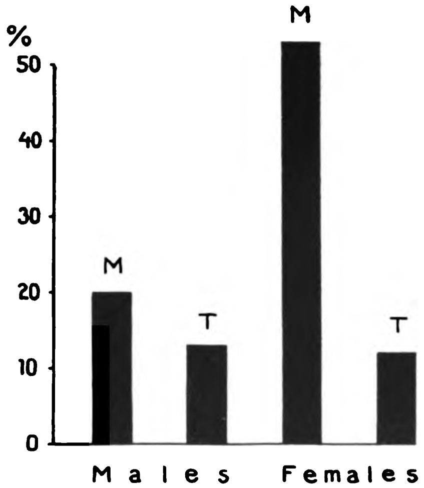
The main reason for the apparently different prognosis of pulmonary tuberculosis in persons with coexistent mental illness or deficiency and in sane tuberculous persons thus seems to be that, in the former category, the tuberculous lesions more frequently reach an advanced stage before they are detected. Some writers have stated that one cause of the difficulty in diagnosing tuberculosis early in mentally disordered persons is that in them tuberculosis runs a comparatively asymptomatic course. This is in agreement with my own observations and may be explained by relative absence of physical exertion in these patients' mode of life. In addition, their capacity to comprehend and communicate any symptoms may be less than in sane persons.

Katz (1952), who made a study of tuberculosis in 27 American mental institutions with a total of 100,000 patients during the period 1941 to



M = mentally ill or deficient mass survey cases
T = total mass survey cases

Fig. 24. Extent of lesions in initially active tuberculosis in cases with coexistent mental disorder and in total mass survey cases.



M = mentally ill or deficient mass survey cases
T = total mass survey cases

Fig. 25. Tuberculosis mortality in cases with coexistent mental disorder and in total mass survey cases (initially active tuberculosis).

1949, concluded that "tuberculosis survival rates among mental patients are probably similar to those among sane tuberculous patients". From my own experience as tuberculosis consultant to a large mental hospital for 6 years I believe that, provided tuberculosis is detected in the same stage, its prognosis is similar in mental patients and in the general population. The increased difficulties of active therapy against tuberculosis in mentally ill or deficient persons are now largely compensated by the availability of specific drugs.

CHAPTER XI

LESIONS NOT INITIALLY REGISTERED AS PULMONARY TUBERCULOSIS AFTER DETECTION BY MASS SURVEY

1. *Material and method*

In addition to the cases of pulmonary tuberculosis which were immediately notified and registered, the mass radiographic survey revealed a group of cases which were judged not to be notifiable but were placed under dispensary supervision. The lesions in these cases were only suspected to be tuberculous or, if "manifestly healed" tuberculosis was considered to be the most likely diagnosis, other circumstances motivated observation. In his 1949 report of this survey, *Mascher* classed 242 cases as non-notifiable (table 3). To them have now been added the 31 persons who at the time of the 1949 report were not followed up (p. 20) and 4 who were missed in this original report. From the total group I have deducted 2 cases of pneumoconiosis for the reason stated concerning this disease in the notified cases.

The group placed under medical supervision but not initially registered thus comprised 275 persons — 136 males and 139 females.

These patients were followed up in the same way as were the registered cases of tuberculosis.

2. *Results*

In figure 26 all 275 cases are shown according to age groups and retrospectively established diagnoses. Twelve persons were thereby considered to have had *active* pulmonary tuberculosis at the time of diagnosis by mass radiography. As in the initially registered cases, the non-registered group contained some cases in which pulmonary tuberculosis was not active at diagnosis, but was *later active*. This group consisted of 21 patients, 12 of whom were men. Tuberculosis which showed *no activity* throughout the observation period was present in 199 cases, 95 of them men. The remaining 21 men and 22 women were found to have *no pulmonary tuberculosis*. Instead, conditions such as sarcoidosis, transient and persistent nonspecific affections and healed hilar and pleural lesions were present in these patients.

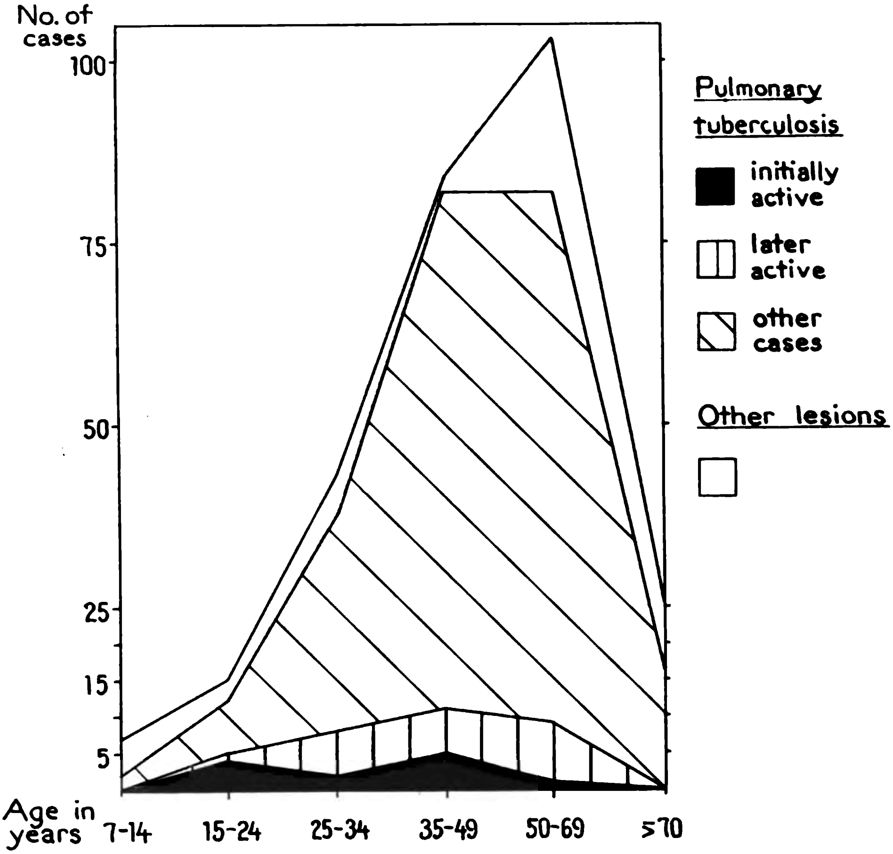


Fig. 26. **Age and final diagnosis in cases not initially registered as pulmonary tuberculosis after detection by mass survey.**

The *initially active* cases are presented in table 47. Most of them had minimal tuberculosis. In 6 of the 12 cases the pulmonary lesions progressed during the first year after diagnosis. (For definitions of grades of progression and regression, see p. 68). The course of the individual cases can be traced in table 47. It is seen that in some of them the course was serious and active therapeutic measures were required. In Case 8 the lesions were originally described as probably nontuberculous, but they led to death within 2 years after diagnosis. This patient also was mentally ill.

The composition of the group in which tuberculosis was not active at diagnosis but was *later active* is seen in table 48. The retrospective evaluation of activity at diagnosis and the interval to "definite activity" are

Table 47. *Cases in which Retrospective Analysis Showed "Suspected" Tuberculosis to Have Been Active at Time of Mass Survey*

Case no.	Findings at mass survey			Roentgenographic progression, years after diagnosis					Bacteriologic findings after diagnosis	Remarks
	Age	Extent of lesions	Bacteriologic findings	<1	1—2	2—3	3—4	6—7		
Males										
1	20	Minimal I	g. w. neg.	+	+				no tests	Subsequent regression (—)
2	30	» I	no tests	+			+++	+++	sputum pos. 2nd year	Bilateral segmental resection
3	44	» I	g. w. neg.	+			+++	+++	» » 4th »	Right artificial pneumothorax, left segmental resection
4	21	» II	no tests						no tests	Subsequent regression (— —)
5	41	» II	g. w. neg.	+					» »	Died of diabetes 5th year
6	37	» II	no tests	+				+++	g. w. pos. 7th year	Artificial pneumothorax
7	34	Mod. adv.	» »			+++			sputum pos. 1st year	Bronchial tuberculosis 1st year, bilateral artificial pneumothorax
8	48	Far adv.	» »		+++				» » 2nd »	Mentally ill. Lesions initially regarded as probably nontuberculous. Died of tuberculosis 2nd year.
Females										
9	27	Minimal I	g. w. neg.		+		+		g. w. pos. 6th year	Subsequent regression (—)
10	62	» I	no tests			++			sputum pos. 3rd year	Irregular follow-up, severe polyarthritis
11	20	» II	g. w. neg.						no tests	Subsequent regression (— —)
12	43	Mod. adv.	g. w. neg.	++					sputum pos. 1st year	Bronchial tuberculosis 1st year, subsequent regression (— —)

g. w. = gastric washings
sputum = direct sputum smear, except in Case 10, in which testing was by culture.

Table 48. *Age at Diagnosis in Cases with "Later Activity"*

Initial status (modified NTA classification)	Age at diagnosis				Total
	15—24	25—34	35—49	50—69 years	
Minimal I	1	3	2	1	7
Minimal II		1	2	2	5
Moderately advanced		2	2	4	8
Far advanced				1	1
Total	1	6	6	8	21

Table 49. *Cases with "Later Activity": Initial Status and Interval between Diagnosis and Signs of Activity*

Initial activity of lesions	Modified NTA classification	Interval from diagnosis to definite activity						Total
		< 1	1—2	2—4	4—6	6—8	>8 years	
Probably active .	Minimal I		1			1		2
	Minimal II		1	1	1			3
	Moderately advanced	1			1	1		3
	Far advanced		1					1
Probably inactive	Minimal I			1		2		3
	Minimal II	1		1				2
	Moderately advanced		1	2				3
Inactive	Minimal I				2			2
	Moderately advanced				1		1	2
Total		2	4	5	5	4	1	21

shown in table 49. This interval implies the time between diagnosis by mass radiography and roentgenographic progression of the pulmonary lesions. In 1 case, however, tests of gastric washings revealed tubercle bacilli before roentgenographic progression was seen, and the interval was calculated to the date of the positive bacteriologic test. In 3 cases progression of parenchymal lesions occurred in association with exudative pleurisy 3, 4 and 6 years, respectively, after the mass survey diagnosis. In another patient progression followed partus. Artificial pneumothorax was induced about 2 years after diagnosis in 1 patient and another was submitted to lobectomy after c. 7 years. A 61-year-old woman, who at the

time of the mass survey had moderately advanced pulmonary lesions and sputum negative for tubercle bacilli on culture, developed cavitary progression with sputum positive on direct microscopy after about 4 years and died of pulmonary tuberculosis a few months later. This patient also had severe polyarthritis. Of these 21 patients, 6 had been freed from medical supervision 1 to 4 years before the tuberculous progression was discovered.

3. *Discussion*

As already mentioned, the boundary between registrable cases of tuberculosis and other positive roentgenographic findings may be difficult to establish. In cases of the latter type, however, the possibility of observation without registration reduces the drawbacks of this difficulty.

The films from the mass radiographic survey of Södermanland County were evaluated by highly experienced physicians. In my retrospective assessment only 12 cases, 9 of them with minimal tuberculosis, of the 275 initially classed as non-notifiable were found to have been active at diagnosis. It is a general experience that, as in my study, the course of minimal tuberculosis frequently is difficult to predict. Of the 21 cases without activity at diagnosis but with later activity more than half, as in the corresponding category of registered cases shown in table 45, had minimal tuberculosis.

In most cases of non-registered pulmonary lesions the suspicion of inactive tuberculosis was confirmed.

CHAPTER XII

COMPARISON BETWEEN TWO MASS SURVEYS WITH A SEVEN-YEAR INTERVAL

Two mass radiographic surveys have been made of the population of Södermanland County.

The first survey, from 1946 to 1948, = MR I.
The second survey, from 1953 to 1955, = MR II.

For comparison between the results of two mass radiographic surveys of the same population at different times, it would be ideal if both surveys could be restricted to the same persons. However, since populations constantly undergo changes due to persons moving in and out and to births and deaths, a comparison of this type is scarcely feasible. Satisfactory information may nevertheless be obtained by comparing two general population surveys made in the same district and with participation rates as close as possible to one hundred per cent.

1. *The tuberculosis situation at commencement of the second survey*

In the interval between the two surveys urbanization and industrialization continued to increase in Södermanland County, and at the latest census (in 1950), 63 per cent of the population lived in built-up areas, as compared with 58 per cent in 1945 (Holm 1956).

The register of pulmonary tuberculosis for the country as a whole showed 8.1 per thousand of the population in 1952, the year before MR II, i.e., only slightly less than the figure for the year before MR I (8.9 per thousand). In Södermanland County itself, 6.2 per thousand of the population were registered as having pulmonary tuberculosis in 1952. Other comparative data concerning the year immediately preceding the respective mass radiographic investigations in Södermanland were as follows.

	Sweden		Södermanland County	
	1952	1945	1952	1945
New notifications of pulmonary tuberculosis				
Number	5,438	9,638	89	156
Per thousand population	0.76	1.45	0.41	0.79

	Sweden		Södermanland County	
	1952	1945	1952	1945
Deaths from pulmonary tuberculosis				
Number	1,089	3,781	30	87
Per thousand population	0.15	0.57	0.14	0.43

As for the year 1945 (fig. 1, p. 18), a diagram for 1952 shows the age distribution of the patients discharged during that year following first hospitalization for intrathoracic tuberculosis (fig. 27). The figures concern the whole of Sweden. The decline in morbidity is clearly seen when the two graphs are compared. The peak of incidence at 20 to 25 years in 1945 is almost flattened out in 1952 and there is an especially marked shift towards higher ages in male patients. This latter observation may be partly explained by an increased number of sanatorium beds available for elderly persons as a result of reduced hospitalization needs in younger age groups.

The newly detected and notified cases of pulmonary tuberculosis in Södermanland County in 1952 are presented according to age in figure 28, which may be compared with the findings for 1945 in figure 2 (p. 18). The age changes in this category of patients were similar to those in the above-mentioned hospitalized cases.

2. *Method, participation rate and positive findings in the second survey*

The second mass radiographic study of Södermanland County took place from August, 1953 to March, 1955 and was carried out according to the same principles as the first survey.

Of the 198,150 persons called to examination, 191,724 responded, making a participation rate of 96.8 per cent. In a further 2.1 per cent there were valid reasons for nonattendance. The remaining 1.1 per cent were considered to have defaulted without valid reason.

The Royal Medical Board's Mass Radiography Centre, where the survey films were primarily examined, referred approximately 4.5 per cent of all these films to the central tuberculosis dispensaries in Södermanland for further scrutiny or investigation. By comparisons with earlier films, mainly from the mass survey in 1946 to 1948, the number of cases requiring closer investigation was reduced to c. 1.5 per cent of the total examined by mass survey.

As in the previous survey (MR I), the cases of manifest or suspected pulmonary tuberculosis were classed as notifiable (registered) or non-notifiable. The observation period for MR II ended in September,

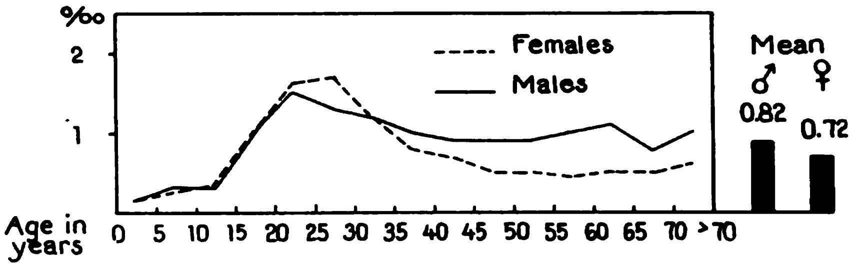


Fig. 27. **Age of patients discharged during 1952 in Sweden from first hospitalization for intrathoracic tuberculosis (in ‰ of age groups in Swedish population).**

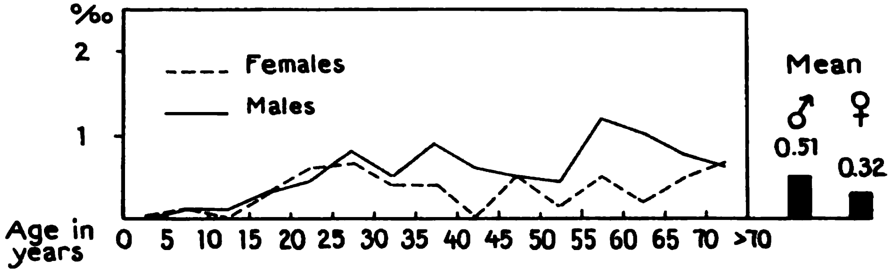


Fig. 28. **Age of patients notified during 1952 in Södermanland as having pulmonary tuberculosis (in ‰ of age groups in Södermanland's population).**

1957, and the duration of follow-up thus ranged from 2 ½ to 4 years. Although this time was too short for direct comparisons with MR I concerning long-term prognosis, I considered that findings after the same observation period in tuberculosis detected by MR I might serve to illustrate the altered long-term prospects for the cases in MR II.

The activity of pulmonary tuberculosis at diagnosis (initial activity) in MR II was, as in MR I, estimated by retrospective study of all the findings in the individual cases. Also in the other aspects studied the case material from MR II was investigated and judged in the ways used in the cases from MR I.

Only those cases which were notified and registered as pulmonary tuberculosis will be presented here. The principles for notification were stated on page 16.

As the result of MR II, 293 persons were registered as having pulmonary tuberculosis. Fifteen of them were excluded from this study, however, for reasons which were elucidated by the retrospective scrutiny: In some of these cases the lesions proved to be nontuberculous, in others

TABLE 50. *Participation in Both Mass Surveys*
(by initially active cases in MR II)

Participants in MR I and MR II	No.	%
Negative film or healed lesions reported from MR I:		
Confirmed by re-scrutiny of film	115	56.4
Absence or healing of lesions doubtful on re-scrutiny	9	4.4
Already on tuberculosis register or under observation at MR I	13	6.4
Registered as pulmonary tuberculosis as result of MR I	6	2.9
Placed under observation as result of MR I	4	2.0
Total participating in 2 surveys	**147**	72.1
Participants only in MR II		
Not resident in Södermanland County at MR I	52	25.5
Less than minimum age (7 years) for examination at MR I	3	1.5
Refused examination at MR I	1	0.5
Total participating only in second survey	**56**	27.5
Not known if participant in MR I	**1**	0.5
Total cases	**204**	

tuberculosis was complicated by pneumoconiosis, and in yet other cases the disease was already known elsewhere.

The clinical material from the mass survey of 1953 to 1955 thus comprised 278 persons who were initially registered as having pulmonary tuberculosis.

3. *Participation in both surveys (by initially active cases from the second survey)*

In a special enquiry the patients found to have active tuberculosis in MR II were investigated concerning participation in MR I and, in such case, how their films from MR I were evaluated. The results are presented in table 50, which also shows the reasons for nonparticipation in MR I.

It is seen that of the persons in whom active tuberculosis was detected at MR II, 72.1 per cent had also been examined in MR I. In 1 case information regarding MR I could not be obtained and another patient had refused examination then. Twenty-seven per cent thus definitely were examined only in MR II; 25.5 per cent were not resident in Södermanland County when MR I was undertaken and 1.5 per cent then were less than 7 years old — the minimum age for examination. Of the 52 persons who moved into Södermanland after MR I, 23 were of foreign nationality.

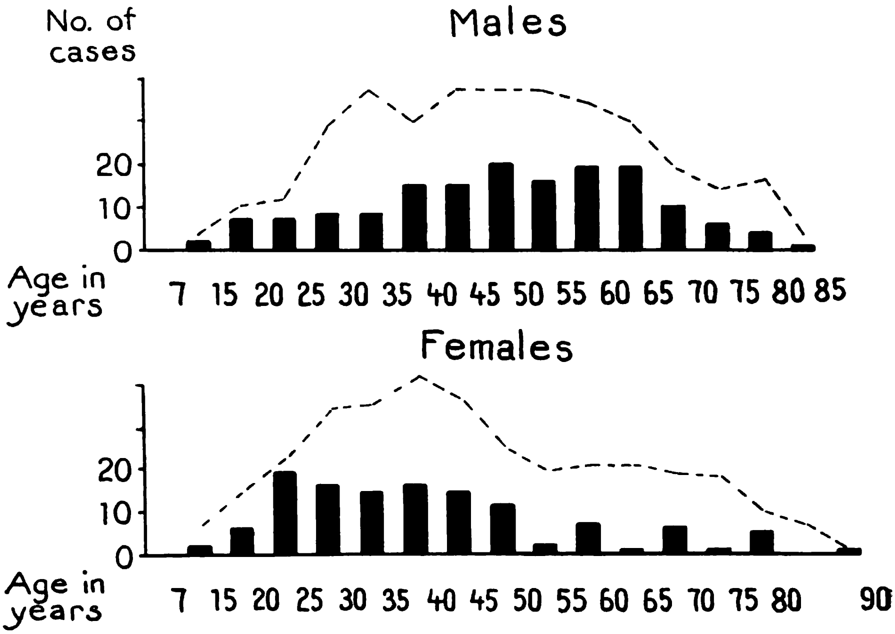


Fig. 29. **Age and sex distribution of notified cases of pulmonary tuberculosis in mass radiography 1953—1955. The interrupted lines show the corresponding cases in mass radiography 1946—1948. See also fig. 6.**

4. *Comparison between cases registered in first and second surveys*

In figure 29 the 278 cases registered as having pulmonary tuberculosis in immediate association with MR II, comprising 157 male and 121 female patients, are distributed into 5-year age groups. The interrupted line above the columns shows the age distribution in the cases registered as the result of MR I. There is an impressive fall in the total number of cases. In the males a pronounced shift towards the higher age groups is seen. The female group shows no major change, but the 19 to 24 age group forms a higher percentage of the series in MR II than in MR I.

In table 51 these age groups are combined into 6 and the initial activity of the cases is also presented (for definitions of activity se pp. 28—29). Cases which the retrospective evaluation showed to have lacked definite activity at diagnosis constituted a considerably smaller proportion of the total series in MR II than in MR I. The main reason was that in many cases a positive finding in MR II, which otherwise might have led to registration, could be compared with a film from MR I and dismissed as not requiring further observation. Of the registered cases without de-

'ABLE 51. *Initial Activity of Lesions in Various Age Groups*

lass Survey 1953—1955

ge in ears	Initial activity of lesions																								Males plus females	
	Active		Initially not active, later active		Probably active (no progression during observation period)		Probably inactive (no progression during observation period)		Inactive (no progression during observation period)		Total		Active		Initially not active, later active		Probably active (no progression during observation period)		Probably inactive (no progression during observation period)		Inactive (no progression during observation period)		Total			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	Males												*Females*													
7—14	1	0.9					1	3.3			2	1.3	2	2.1									2	1.6	4	1.4
5—24	13	11.8					1	3.3			14	8.9	21	22.3	1	100			3	21.4			25	20.7	39	14.0
5—34	12	10.9			2	20.0	2	6.7			16	10.2	22	23.4			3	50.0	2	14.3	3	50.0	30	24.8	46	16.6
5—49	36	32.7	3	100	3	30.0	8	26.7			50	31.8	34	36.2			2	33.3	2	14.3	3	50.0	41	33.9	91	32.7
)—69	41	37.3			3	30.0	17	56.7	3	75.0	64	40.8	11	11.7			1	16.7	4	28.6			16	13.2	80	28.8
≥ 70	7	6.4			2	20.0	1	3.3	1	25.0	11	7.0	4	4.3					3	21.4			7	5.8	18	6.5
otal	110	(70.1)	3	(1.9)	10	(6.4)	30	(19.1)	4	(2.6)	157		94	(77.7)	1	(0.8)	6	(5.0)	14	(11.6)	6	(5.0)	121		278	

lass Survey 1946—1948

otal	171	(48.6)	33	(9.4)	18	(5.1)	59	(16.7)	71	(20.2)	352		168	(51.9)	16	(4.9)	17	(5.2)	52	(16.1)	71	(21.9)	324		676	

he figures in brackets denote % of the total for the sex within the respective groups.

finitely active tuberculosis initially in MR II, 4 showed signs of activity later in the observation period.

The very small number of definitely *inactive* tuberculosis cases which were registered following MR II was to some extent attributable to the shortness of the observation period, which permitted the requisite 5 years of stability only in cases with roentgenograms antecedent to the mass survey.

As a logical consequence thereof, *probably inactive* tuberculosis was considerably more common than inactive lesions in MR II. The numerical relationship of these categories thus alters with the length of the observation period.

The *probably active* group was of similar relative size in both mass surveys (c. 5 per cent of the registered cases).

The *initially active* cases numbered 204, or 73.4 per cent of all the registered cases, in MR II, as compared with 339, or 50.2 per cent, in MR I. They comprised 1.1 per thousand of the examined population in MR II and 1.9 per thousand in MR I.

5. *Comparative analysis of the initially active cases*

Roentgenologic classification. Figure 30 presents the clinical material according to the NTA classification of the extent of pulmonary tuberculosis with my modification in regard to minimal lesions (see p. 30). The groups are divided to show cases with and cases without activity at diagnosis. It is seen that the latter were much less prominent in MR II than in MR I.

The main interest attaches to the extent of active tuberculosis, which may be studied also in table 52. Moderately advanced lesions, in MR II as in MR I, were present at diagnosis in 42.2 per cent of all the active cases. In both surveys, too, about half of the males and one-third of the females had moderately advanced tuberculosis. The total of minimal tuberculosis, on the other hand, increased by about 10 per cent from MR I to MR II. In the males this increase occurred in minimal II, whereas in the females minimal I was the increased category. The far advanced cases were correspondingly decreased — to about half from MR I to MR II. The percentage decrease was only slightly greater in the females than in the males.

In table 52 these NTA groups are further subdivided and the percentage distribution of each subgroup in the two mass survey series may be compared. The shift to milder disease is there expressed as a percentage increase in MR II of most of the noncavitary subgroups. On the

other hand, the far advanced cases plus the cavitary moderately advanced cases decreased from 27.8 per cent in MR I to 18.1 per cent in MR II.

The comparison of the extent of tuberculosis may therefore be summarized by saying that from the first to the second mass survey a shift took place from far advanced towards minimal disease.

Age and sex. The age composition of the initially active cases is illustrated by the curves in figure 31. In addition to the lesser number of cases, a relative shift towards higher age is seen in the male cases. The sharp peak in the age curve of female patients in MR I, with maximum at 30 to 34 years, was lacking in MR II.

Nationality. The number of non-Swedish persons with active tuberculosis rose from 5.6 per cent of the total active cases in MR I to 11.8 per cent in MR II. The increase was mainly caused by Finnish subjects seeking work in Sweden. They comprised only 0.6 per cent of the active cases in MR I, but 5.9 per cent in MR II.

Occupational classification. Like the MR I cases, those found by MR II were classified as economically active or economically inactive, and the former also according to occupation. In both respects there was good conformity between the two survey series. Nine persons whose occupations involved food handling or work with children or sick persons were found to have active tuberculosis at MR II. They constituted 4.4 per cent of the active cases, as compared with the 4.7 per cent found by MR I.

Familial or environmental tuberculosis. Of the initially active cases in the MR II series, 29.9 per cent reported that in parents and/or siblings some form of tuberculosis was or had been present; the figure for MR I was 27.4 per cent. The corresponding frequencies among the total registered cases were 26.3 per cent in the MR II series and 22.1 per cent in that from MR I. Nor was there any noteworthy difference as regards the proportion of other tuberculous relatives or contacts in the two survey series.

Previous manifestations of tuberculosis. In MR II 8.3 per cent of the initially active cases had previously been registered as having postprimary pulmonary tuberculosis, as against 3.8 per cent in MR I. This frequency may be expected to rise in proportion to the extent of earlier investigations for tuberculosis in the population. Thus, in 6 of the 15 active cases in MR II with previous registration as sputum-negative pulmonary tuberculosis this registration had resulted from findings at MR I. Retrospective review, however, showed only 1 of the 6 to have had active lesions at the time of MR I. Pleurisy was included in the anamnesis in 4.4 per cent of the active cases in MR II and in 8.2 per cent of those in MR I. Otherwise the two series were similar as regards previous manifestations of tuberculosis.

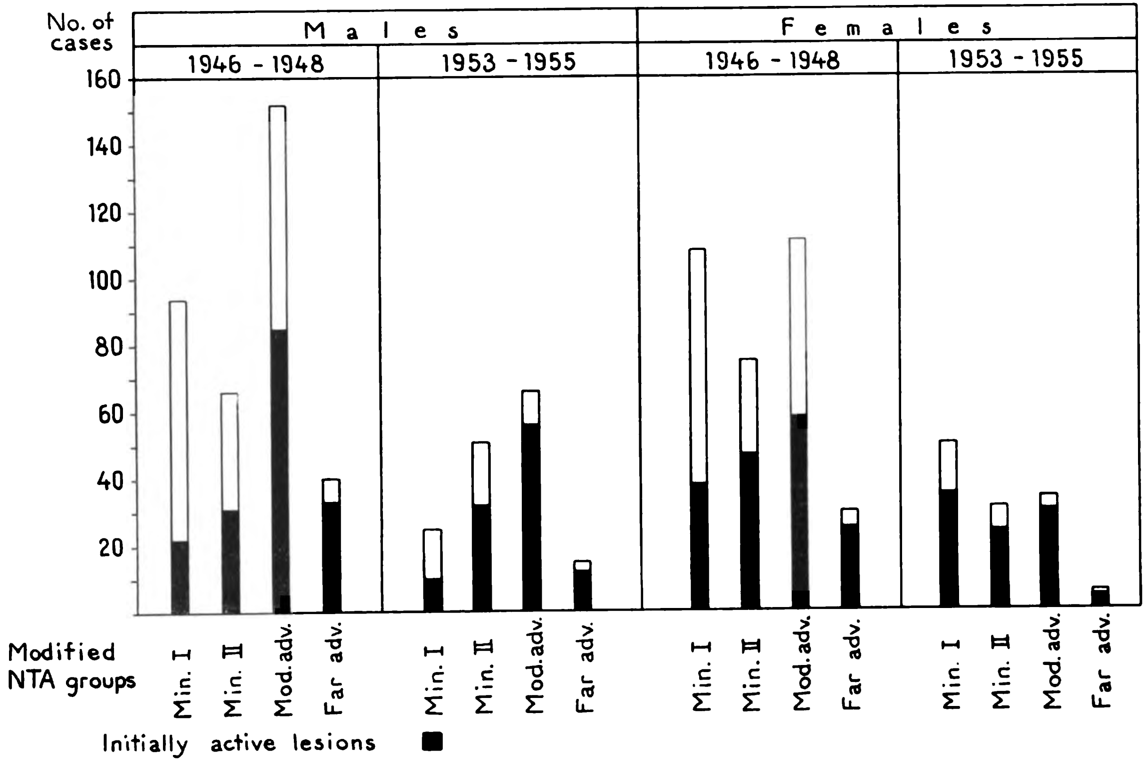


Fig. 30. **Total notified cases and initially active cases in mass surveys 1946—1948 and 1953—1955.**

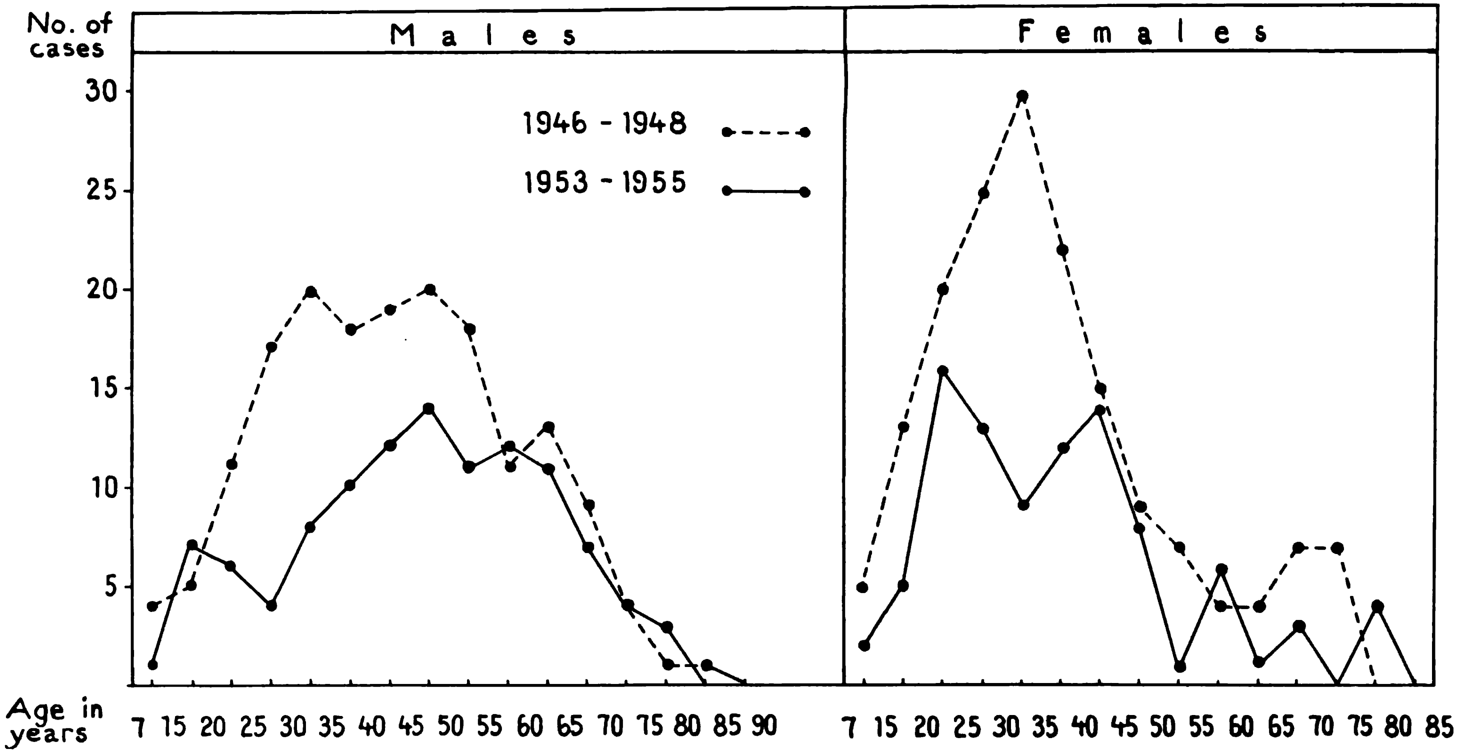
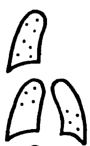


Fig. 31. Age in initially active cases in mass surveys 1946—1948 and 1953—1955.

TABLE 52. *Distribution of Initially Active Cases according to Modified NTA*

Modified NTA groups		Males			Females			Males plus females			Groups
		MR II		*MR I*	*MR II*		*MR I*	*MR II*		*MR I*	
		No.	%	%	No.	%	%	No.	%	%	
					Minimal I						
A		5	4.5	9.9	27	28.7	15.5	32	15.7	12.7	A
B		5	4.5	2.9	8	8.5	7.1	13	6.4	5.0	B
					Minimal II						
C		23	20.9	13.4	17	18.1	16.1	40	19.6	14.8	C
D		5	4.5	2.3	5	5.3	7.7	10	4.9	5.0	D
E	Primary tuberculosis			1.7	1	1.1	3.6	1	0.5	2.7	E
F	Tuberculoma	4	3.6	0.6	1	1.1	0.6	5	2.4	0.6	F
					Moderately advanced						
G		1	0.9	1.2	1	1.1	1.2	2	1.0	1.2	G
H				2.3			1.8			2.1	H
I		18	16.4	11.7	5	5.3	10.7	23	11.3	11.2	I
J		24	21.8	19.3	17	18.1	14.9	41	20.1	17.1	J

MR I = mass radiographic survey 1946—1948
MR II = » » » 1953—1955

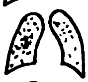
Modified NTA groups		Males			Females			Males plus females			Groups
		MR II		*MR I*	*MR II*		*MR I*	*MR II*		*MR I*	
		No.	%	%	No.	%	%	No.	%	%	
					Moderately advanced (cont'd)						
K		3	2.7	8.2	2	2.1	1.8	5	2.4	5.0	K
L		4	3.6	2.3			3.0	4	2.0	2.7	L
M		6	5.5	2.9	4	4.2	1.2	10	4.9	2.1	M
N				1.7	1	1.1		1	0.5	0.9	N
					Far advanced						
P		3	2.7	3.5	1	1.1	2.4	4	2.0	2.9	P
Q		7	6.4	11.1	3	3.2	8.9	10	4.9	10.0	Q
R				1.2	1	1.1	0.6	1	0.5	0.9	R
S		2	1.8	3.5			1.8	2	1.0	2.7	S
T							1.2			0.6	T
					Total						
Minimal I . . .		10	9.1	12.9	35	37.2	22.6	45	22.1	17.7	
Minimal II . . .		32	29.1	18.1	24	25.6	28.0	56	27.4	23.0	
Mod. advanced .		56	50.9	49.7	30	31.9	34.5	86	42.2	42.2	
Far advanced . .		12	10.9	19.3	5	5.3	14.9	17	8.3	17.1	
Total cases		110		171	94		168	204		339	

TABLE 53. *Initial Bacteriologic Findings in Initially Active Cases*

Initial tests for tubercle bacilli	Males			Females			Males plus females		
	MR II		MR I	MR II		MR I	MR II		MR I
	No.	%	%	No.	%	%	No.	%	%
Positive:									
Sputum, direct smear .	7	6.4	25.1	7	7.6	16.1	14	6.9	20.6
Sputum, culture	4	3.6	0.6	4	4.2		8	3.9	0.3
Gastric washings[1] . . .	60	54.6	22.8	46	48.9	26.8	106	52.0	24.8
Total positive	*71*	*64.6*	*48.5*	*57*	*60.7*	*42.9*	*128*	*62.8*	*45.7*
Negative:									
Sputum, direct smear .			11.1	2	2.1	7.1	2	1.0	9.1
Sputum, culture	3	2.7		1	1.1	0.6	4	2.0	0.3
Gastric washings[1] . . .	34	30.9	33.3	30	31.9	41.1	64	31.4	37.2
Total negative	*37*	*33.6*	*44.4*	*33*	*35.1*	*48.8*	*70*	*34.4*	*46.6*
No test initially	2	1.8	7.0	4	4.2	8.3	6	2.9	7.7
Total cases	110		171	94		168	204		339

MR I = mass radiographic survey 1946—1948
MR II = » » » 1953—1955
[1] culture and/or guinea pig test.

Initial bacteriologic findings. In table 53 the active cases from the two surveys are compared in this respect. The MR II series was somewhat more thoroughly investigated for tubercle bacilli than were the cases from MR I. Thus, bacteriologic studies in association with diagnosis were lacking in only 2.9 per cent of the active cases from MR II, but in 7.7 per cent of those from MR I. Moreover, negative direct microscopy of sputum was accepted as the sole test in 9.1 per cent of the total active cases of the MR I series, but in only 1.0 per cent of the MR II group. A higher frequency of gastric lavage among cases of active tuberculosis ensures a greater number with positive bacteriologic findings. This presumably was why tubercle bacilli were found in 62.8 per cent of the active MR II cases at diagnosis as against 45.7 per cent of those from MR I. The more abundant the presence of tubercle bacilli in the individual cases, however, the more positive direct microscopies may be anticipated in series such as these. In MR II only 6.9 per cent of the active cases initially had sputum positive for tubercle bacilli on direct microscopy, whereas in MR I this frequency was as high as 20.6 per cent. The difference undoubtedly was associated with the higher frequency of advanced tuberculosis in MR I.

TABLE 54. *Initial Erythrocyte Sedimentation Rate in Initially Active Cases*

E. S. R. (mm/1 hour)	Males			Females			Males plus females		
	MR II		MR I	MR II		MR I	MR II		MR I
	No.	%	%	No.	%	%	No.	%	%
Males *Females*									
< 6 <10	36	32.7	30.4	34	36.2	27.3	70	34.4	28.9
6—10 10—15	26	23.6	29.2	23	24.5	22.6	49	24.0	25.9
11—20 16—20	25	22.7	15.2	13	13.8	13.7	38	18.6	14.5
Males and females									
21—30	6	5.5	8.2	11	11.7	14.9	17	8.3	11.5
31—40	5	4.6	4.1			5.4	5	2.4	4.7
41—60	6	5.5	5.3	8	8.5	7.1	14	6.9	6.2
> 60	1	0.9	2.3	4	4.2	4.8	5	2.4	3.5
Not measured	5	4.6	5.3	1	1.1	4.2	6	2.9	4.7
Total cases	110		171	94		168	204		339

MR I = mass radiographic survey 1946—1948
MR II = » » » 1953—1955

Initial erythrocyte sedimentation rate. Normal E. S. R. (Westergren) readings were for present purposes considered to be less than 6 mm/1 hour in males and less than 10 mm in females. Readings between 6 and 10 mm in males and between 10 and 15 mm in females were classed as borderline values. Higher readings were regarded as elevated. The E. S. R. at diagnosis is shown in table 54. Elevated readings were found in 39.2 per cent of the male patients with active tuberculosis in MR II and in 35.1 per cent in MR I, i. e., fairly similar frequencies. Among the females, elevated E. S. R. was somewhat less common in MR II than in MR I, viz., 38.2 and 45.9 per cent, respectively.

Current tuberculous complications. In both mass survey series there was a very low and similar frequency of tuberculous complications at the time of diagnosis. If one includes bronchial tuberculosis among these complications, the total frequency among the active cases was 2.9 per cent in MR II and 5.0 per cent in MR I. Bronchial tuberculosis (in almost all cases bronchoscopically verified) was present in 2.4 per cent of the active cases from MR II and in 3.2 per cent of those from MR I.

Nontuberculous complications. Of the somatic nontuberculous conditions which commonly are considered to be important complications of

tuberculosis, diabetes mellitus was present in 1.0 per cent of the initially active cases detected by MR II and in 2.0 per cent of those from MR I. The corresponding figures for gastric resection were 2.4 and 0.6 per cent. Among the women, 4.2 per cent in the MR II series and 5.4 per cent of the MR I group were pregnant or lactating. The special aspects of tuberculosis in mentally ill or deficient persons are discussed in chapter X. Male patients in this category comprised 10.0 per cent of the males with active tuberculosis in MR II and 11.7 per cent in MR I. The respective frequencies among the female patients were 4.3 and 10.1 per cent.

6. *Follow-up of the initially active cases*

The retrospective review of the cases of tuberculosis discovered by the second county-wide mass radiographic survey was made, as already stated, in September, 1957. The follow-up period of 2 ½ to 4 years thus precluded direct comparison with the first survey as regards long-term prognosis. Nevertheless, in this relatively short time data were available which, when compared with findings from the same period after MR I, show the changed tuberculosis situation in Södermanland County and also yield indications of the expected long-term prognosis for the cases detected by MR II.

The comparisons which now follow concern mainly the longest period for which the entire MR II series could be followed up, viz., 2 ½ years. The figures for the last half year of this period were obtained in MR I by halving the values for the third year of observation and in MR II by direct recording.

A. **Roentgenographic progression and mortality**

The roentgenographic status for each year in the individual patients was compared with that in the previous year, and the difference was graded according to the principles stated on page 68. The most suitable basis for comparison between the roentgenographic changes in the cases of active tuberculosis discovered by the two mass surveys seemed to be progression. Three grades of progression were recognized, of which + + + denoted development of pulmonary cavity. The following figures show the frequency of roentgenographic progression during 2 ½ years after MR I and MR II. Each case is included once only, viz., with the highest grade of progression seen during the observation period.

	MR II No.	MR II %	MR I No.	MR I %
Progression +	51	25.0	67	19.8
» ++	8	3.9	19	5.6
» +++	21	10.3	58	17.1
Total cases with progression during 2 1/2 years	*80*	*39,2*	*144*	*42.5*
Deaths from pulmonary tuberculosis	1	0.5	27	8.0

Cavitary progression was not confined to cases in which tuberculosis was advanced at diagnosis. Of persons with minimal lesions when first seen, 10 of the 101 (9.9 per cent) in MR II and 13 of the 138 (9.4 per cent) in MR I developed cavitary progression in the first 2 1/2 years after diagnosis.

The higher frequency of the more severe grades of progression in the MR I series is illustrative of the considerably graver nature of the general tuberculosis situation in the county at that time.

Mortality from pulmonary tuberculosis was considerably higher among the cases found at MR I than in the MR II group. Of the patients with active tuberculosis at diagnosis, 27 (8.0 per cent) of the MR I series died of the disease within 2 1/2 years, but only 1 (0.5 per cent) of the MR II series. This last patient was a 77-year-old woman who also had diabetes mellitus. The death in the fourth year of observation of a 76-year-old man from MR II brought the tuberculosis mortality rate in that series up to 1.5 per cent; the figure for the same period after MR I was 10.7 per cent.

Death from other causes than pulmonary tuberculosis occurred in the first 4 years of observation in 2 cases with active tuberculosis from the MR II group and in 13 of those from MR I. The fatal disease in the first 2 patients, who were elderly, was cardiovascular.

B. Bacteriologic studies

Many factors influence the initial frequency of positive tests for tubercle bacilli. Difficulty in obtaining positive results may be partly attributable to such factors as the facilities for investigation and the distance which the patient must travel to be examined.

It was shown in table 53 that of the patients with active tuberculosis at diagnosis, 62.8 per cent from MR II and 45.7 per cent from MR I also had positive bacteriologic findings. These figures included positive sputum tests (direct microscopy or culture) in 10.8 per cent of the MR II cases and in 20.9 per cent of those from MR I. Further positive results

TABLE 55. *Therapy in Initially Active Cases*

Treatment during observation period	2 1/2 years after mass survey			4th year after mass survey		
	MR II		MR I	MR II		MR I
	No.	%	%	No.	%	%
Sanatorium care	147	72.1	61.7	95	73.1	66.1
Artificial pneumothorax	15	7.4	25.1	7	5.4	26.8
Thoracoplasty	1	0.5	2.4	1	0.8	3.0
Pulmonary resection	8	3.9		6	4.6	
Specific drugs	174	85.3	11.8	114	87.7	20.4
Total cases	204		339	130		336

MR I = mass radiographic survey 1946—1948
MR II = » » » 1953—1955

during 2 ½ years of observation caused the respective figures to rise to 15.2 and 24.8 per cent.

In the remaining cases, i. e., those in which tubercle bacilli were not demonstrated in the sputum, gastric lavage should therefore with few exceptions have been desirable. Such tests were very extensively made -- in 98.8 per cent of the relevant cases from MR II and in 85.1 per cent of those from MR I. In MR II bacteriologic investigation thus was almost as complete as possible and also the MR I series was very well investigated from this aspect.

After 2 ½ years tubercle bacilli had been demonstrated in 72.5 per cent of the MR II cases and in 57.2 per cent of the MR I cases with active tuberculosis. In considering this higher percentage in MR II one should take into account the greater number of persons examined by gastric lavage in MR II (table 53) and the greater proportion of hospitalized cases (table 55) which permitted more frequent tests.

C. Treatment

The change which has taken place in the tuberculosis situation is reflected not least in the frequency with which the various forms of therapy are employed. Table 55 shows a comparison in this respect between all the initially active cases of the 2 survey groups after 2 ½ years of observation and between the 130 MR II cases and the 336[1] MR I cases which could also be followed up to the fourth year after diagnosis.

[1] Of the original 339 cases, 2 had emigrated and 1 (with a primary focus) was released from supervision.

The tendencies in both comparisons are similar. The cases detected by MR II received much more antimicrobial medication but much less artificial pneumothorax and thoracoplasty, while pulmonary resection was performed only in the MR II cases, viz., in 3.9 per cent within 2 ½ years. The increased proportion of hospitalized patients (from 61.7 per cent in MR I to 72.1 per cent in MR II after 2 ½ years) must be considered partly attributable to the increased number of beds which have become available even for patients in the higher age groups, mainly because of the general decline in tuberculosis morbidity. Elderly patients discovered to have pulmonary tuberculosis at MR I were very often cared for in their homes.

7. *Discussion*

As mentioned in the introduction to this chapter, ideally representative material for comparison between the results of two mass radiographic surveys of the same catchment area at different times is almost precluded by the normal changes in population composition and the difficulties of approaching 100 per cent participation. In the two county-wide surveys of Södermanland the respective participation rates were 96.7 and 96.8 per cent. The population changes are illustrated by the increase from MR I to MR II of about 20,000 inhabitants in the ages covered by the mass surveys and by the fact that, of the cases of active tuberculosis detected at MR II, one-fourth were not residents of Södermanland County at the time of MR I.

For many reasons, which will not be discussed here, the tuberculosis situation in Södermanland altered essentially in the time between the two mass surveys, i.e. a mean of 7 years. Of the cases which were notified as the immediate result of the survey films, 339 from MR I and 204 from MR II had active tuberculosis at diagnosis. These constituted, respectively, 1.9 and 1.1 per thousand of the examined population. (The few cases which were complicated by pneumoconiosis are excluded here.) This reduction must in itself be regarded as an expression of the improved tuberculosis situation. Further, analysis of the active cases showed a shift towards roentgenographically less extensive disease in MR II. The lower frequency of positive direct microscopy for tubercle bacilli in the cases from MR II was likewise a pointer to milder disease.

The relative shift towards higher age groups in new cases of pulmonary tuberculosis in Sweden, which was discussed in an earlier paper *(Källqvist 1956)*, was also evident from MR I to MR II.

Follow-up study was made after 2 ½ years of all the initially active cases and after 3 to 4 years of a reduced number of these. Cavitary progres-

sion of the pulmonary lesions was appreciably more frequent in the MR I cases than in those discovered by MR II. More impressive, however, was the reduction in early deaths from pulmonary tuberculosis. After 2 ½ years 8 per cent of the MR I cases were dead of this cause, but only 0.5 per cent of those from MR II.

The improved therapeutic possibilities were exploited in the MR II series in the form of more frequent hospitalization, increased administration of specific drugs, and use of pulmonary resection. One may wonder why only 88 per cent of the patients found at MR II to have active tuberculosis received specific medication, since access to such drugs was virtually unrestricted. The main reason was that in some cases the diagnosis of activity was first made after a period of observation, during which the lesions could undergo spontaneous regression, thus rendering medication superfluous. A few patients were offered but refused such treatment.

The increased frequency of hospitalization after MR II must be considered in the light of the general decline in tuberculosis morbidity. One result of this decline has been release of hospital beds for some types of cases which would not have been hospitalized after MR I, particularly elderly patients who would have been regarded as unsuitable for active therapy and would not have come into question for the then relatively scarce specific drugs.

Despite the reduction in the number of cases of active tuberculosis detected at MR II in comparison with MR I, it is clear that the routine measures against tuberculosis in Södermanland County were not adequate for early detection of all cases of active pulmonary tuberculosis. The incidence of tuberculosis in Södermanland, however, is among the lowest in Sweden and the relatively rapid decline of all notifications of pulmonary tuberculosis is evident from figure 3 (p. 25). This diagram also shows that only at the time of the mass radiographic surveys did the notifications per thousand population in Södermanland County reach up to or exceed the figures for the whole of Sweden.

This falling frequency may well evoke the question of the future justification of county-wide mass radiography. Such surveys demand much expenditure of money and labour, a great deal of the latter voluntarily supplied. There has been lively speculation concerning how many cases a mass radiographic survey should reveal in order to justify its expense. It has been stated that even a very small number may suffice, as the early detection should save the community the high cost entailed by treatment of advanced tuberculosis and by the disablement which may ensue. Obviously, the *number* of cases which an investigation reveals should not be the sole criterion of its value. Mass radiography must be regarded also as a prophylactic measure in that it can detect previously unknown infectious tubercu-

losis, which is the most dangerous potential source for the spread of infection.

One must further keep in mind that the incidence of tuberculosis may rise again if, for instance, there is immigration from other countries in which the disease is more common.

If for county-wide mass radiography were substituted the increasingly common group examinations in, for instance, schools, workplaces and military personnel, there would still remain the difficulty of reaching some categories of the population, such as the elderly and younger persons who do not work outside the home.

In my opinion, therefore, the time has not yet come to cease county-wide mass radiography, even in Södermanland, but it is possible that a transition can gradually be made to periodic examination of the groups in which tuberculosis in most frequently seen. Such group studies, of course, should be extended to include persons who, by reason of their occupations, are especially liable to spread infection.

On the credit side of mass radiography must also be placed its considerable value in disclosing other intrathoracic disease than tuberculosis. Cardiac disorders, benign tumours and the increasingly common malignant growths suffice as examples.

SUMMARY

CHAPTER I

The evolution of mass miniature radiography as a valuable method of tuberculosis case finding in population groups was traced. After a brief review of immediate results from some Swedish mass radiographic studies, prognostic findings were presented from such surveys in Sweden and elsewhere. Community-wide surveys in particular tend to be hampered by difficulties in reaching high participation rates and in tracing cases for follow-up. In countries where frequent registration of the population is compulsory, as in Sweden, follow-up investigation is greatly facilitated.

In the few reports in the literature which describe prognostic comparisons between cases of tuberculosis detected by mass radiography and "control" cases, the former category invariably had much better prognosis. Detailed comparison between such reports is difficult, however, because of differences in, *inter alia,* composition of the materials and in diagnostic and prognostic criteria.

CHAPTER II

In Sweden all cases of tuberculosis must be notified and registered, except when the lesions are manifestly healed.

CHAPTER III

The first mass radiographic survey of the general population of Södermanland County took place from October, 1946 to January, 1949. At the end of the year preceding the survey, 4.1 per thousand of the population of Södermanland were on the register of persons with pulmonary tuberculosis. Although examination was voluntary, 96.7 per cent (178,344 persons) of the population aged 7 years or more attended. At the Royal Medical Board's Mass Radiography Centre 13,905 photofluorograms were judged to show healed intrathoracic tuberculosis. In addition, 5,667 films were referred to the central tuberculosis dispensary in Södermanland for further evaluation or investigation.

CHAPTER IV

As a direct result of the mass survey, 676 persons were notified and registered as having pulmonary tuberculosis and 275 were placed under supervision but were not considered to be notifiable. For prognostic comparison with the registered cases were used 292 cases of pulmonary tuberculosis which derived from the same population and were consecutively diagnosed during the same period as the mass survey, but independently of it.

CHAPTER V

The registered cases from the mass survey and the control series were classified according to activity of tuberculosis at the time of diagnosis. This classification was made by retrospective study of all available data in each case. The categories were active, inactive, probably active and probably inactive. From the last three groups were extracted cases which showed definite activity later in the observation period. These "later active" cases formed a special group.

The cases were further classified according to roentgenographic extent of pulmonary tuberculosis at diagnosis. The NTA (National Tuberculosis Association, U. S. A.) grades of minimal, moderately advanced and far advanced were used, but were further subdivided.

The activity of tuberculosis was studied in relation to roentgenographic extent of the lesions and to age and sex. The percentage of cases active at diagnosis ("initially active") increased with the extent of the disease. Among such cases advanced tuberculosis was considerably more common in the control series than in the survey series. Moderately advanced and far advanced tuberculosis together comprised 73 per cent of the control series as against 59 per cent of the survey group. The respective frequencies of far advanced tuberculosis were 41 per cent and 17 per cent. Pulmonary excavation was demonstrated in 21 per cent of the initially active survey cases and in 45 per cent of the active controls.

As regards age distribution in these active cases, the most marked difference concerned patients younger than 25 years, who were more numerous among the controls (34 per cent of the males and 39 per cent of the females) than among the survey cases (12 per cent of the males and 23 per cent of the females). Male patients aged 50 years or over formed a somewhat higher proportion of all males with active lesions in the survey series than in the control series (33 and 25 per cent, respectively). In both series about 18 per cent of the females with active tuberculosis were 50 years or older.

Because of the relatively high frequency of "nonactive" tuberculosis in the cases diagnosed by mass radiography, the proportion of patients aged 50 or over rose in the total of registered cases to 45 per cent of the males and 36 per cent of the females. This first mass survey of Södermanland County therefore revealed many tuberculous lesions in middle-aged or elderly persons, but retrospective evaluation showed that active disease was less common in these age groups than in younger persons.

The sex distribution of the initially active cases was strikingly even. The survey series thus comprised 171 males and 168 females and the control series contained 126 males and 122 females. In the total of cases registered as the result of mass radiography, 49 per cent of the males and 52 per cent of the females had active tuberculosis at diagnosis. The corresponding figures in the total control series were 86 per cent and 84 per cent. This disparity was a natural consequence of the different methods of diagnosis.

CHAPTER VI

In the continued comparative analysis of tuberculosis cases registered immediately after mass radiography and control cases, most interest was attached to the *initially active* cases. Tuberculosis which became active later was presented separately, but the other categories of activity were combined into a single group.

Of these initially active cases, about 95 per cent in the survey series and in the control series were Swedish by birth. Between the two series there was good agreement as regards the patients' occupations. Familial tuberculosis was more common in the control series. This preponderance could be explained by the cases which were diagnosed following routine examination of contacts. Previous manifestations of tuberculosis were likewise more common among the controls, one reason being that in some cases pulmonary lesions were discovered at routine examination in connection with previous or current nonpulmonary tuberculosis. The tests for tubercle bacilli which were made in association with diagnosis were more frequently positive in the control series, as the result of their preponderance of advanced disease. This poorer average status also entailed higher frequency of elevated E. S. R. Coexistent extrapulmonary tuberculosis, mainly pleural, laryngeal or intestinal, was more commonly found in the control cases than in the survey cases. Nontuberculous complications were relatively rare in both series, except for mental illness and deficiency, which were more frequent among the survey cases and are discussed in chapter X.

All these discrepancies between the mass survey and the control series could be attributed to the difference in the method of diagnosis.

CHAPTER VII

While the reason for diagnosis was uniform in the mass survey cases, it varied widely in the control series. Of the controls with active tuberculosis at diagnosis, 71 per cent sought medical advice for symptoms of pulmonary or other tuberculosis. In a further 6 per cent pulmonary tuberculosis was discovered at examination for nontuberculous disease, in 11 per cent at examination of contacts of tuberculous persons, and in 12 per cent at routine health control investigations. Approximately one-third of all the patients with active tuberculosis sought advice for cough with or without pyrexia and night-sweats, and in 13 per cent the presenting symptom was haemoptysis.

The reasons for diagnosis were in good conformity with those reported from a similar Swedish series of cases from the period 1946 to 1950. This similarity indicated that my control material was representative of pulmonary tuberculosis detected by routine measures at the time in question.

CHAPTER VIII

In all cases follow-up ended in January, 1957. The length of the observation period thus ranged from at least 8 to more than 10 years, or until pulmonary tuberculosis was considered to be cured, or until death.

Clinical observations during the follow-up period concerned roentgenographic progression and regression, mortality, bacteriologic tests, the frequency of various therapeutic measures, the interval from diagnosis to institution of treatment, and complications of treatment. Where appropriate, the duration of treatment was also investigated.

After 8, 9 and 10 years comparison was made between the initially active cases in the registered survey series and in the control series as regards medical status and fitness for work.

A *statistical* analysis of the medical results after 8 years complemented this clinical comparison. As the composition of both series of cases was highly heterogeneous, it was necessary first to determine which factors were most important for their particular prognosis.

In material such as mine, however, factors which affect prognosis usually are closely correlated with each other and direct comparisons between heterogeneous groups can give misleading results. I therefore considered it necessary to use a method which permits evaluation of the importance of single factors independently of correlated factors. For this purpose the "homogenization" method was deemed suitable. It implies that the case material is subgrouped according to the results of a preliminary analysis, and that frequencies (p) within these subgroups are transformed to the

function $\varphi = 2$ arc sin $\sqrt{p}$. The difference in φ values is calculated between subgroups differing only as regards the factor under test and a weighted mean is taken of these differences.

In the present investigation the method permitted presentation of the effects of the principal prognostic factors, and of differences between mass survey material and control material homogenized for these factors, in clear and simple diagrams.

CHAPTER IX

Initially active tuberculosis

The total of initially active cases was 339 in the mass survey series of registered cases and 248 in the control series.

Roentgenographic progression and regression were studied from two angles, qualitative and quantitative. In the qualitative analysis each case could appear no more than once in each respect, viz., showing the highest degree of progression and the extreme of regression which occurred during 8 years. Cavitary progression occurred in all the roentgenographic groups of cases used for the investigation. The frequency of cavitary progression was similar in the survey cases and in the controls; it was 11 to 17 per cent in minimal tuberculosis, c. 30 per cent in moderately advanced disease and 65 to 70 per cent in the far advanced groups. Regression was also similarly distributed in the two series of cases. The highest frequency of cavity closure was seen in cavitary moderately advanced tuberculosis, the group which received most collapse therapy.

The quantitative analysis of roentgenographic progression and regression illustrated the annual frequency of these changes within the respective roentgenographic groups. Each case could therefore appear more than once. On the whole the results were similar in the mass survey series and in the controls. As regards progression in far advanced tuberculosis during the first year after diagnosis, however, the control cases showed greater frequency than did the survey group. Statistically this difference was highly significant.

Mortality from pulmonary tuberculosis was much higher in the control series than in the survey series. During the first year after diagnosis 21 per cent of the controls died of this cause, but only 4 per cent of the survey group. The difference was mainly due to higher first year mortality in the far advanced controls (44 per cent) than in the same roentgenographic group from the survey series (19 per cent).

Bacteriologic studies were extensively made. At the end of 8 years only 7 survey cases and 6 controls had not been so examined. Tubercle bacilli

were demonstrated at some time during this period in 66 per cent of the cases in the survey group and in 76 per cent of those in the control group.

The most common form of *treatment,* sanatorium care, was given at some time during the observation period to 71 per cent of the survey cases and to 87 per cent of the controls. Also as regards duration of hospitalization, there was some predominance in the control series.

Specific antimicrobial agents were so scarce at the beginning of the investigation that, for instance, only 8 survey cases and 11 controls received such medication during the first year after diagnosis. About 35 per cent of both series received specific drugs at some time in the observation period.

Artificial pneumothorax was the most common form of active therapy at the time in question. It was most frequently used in cavitary moderately advanced tuberculosis — in c. 60 per cent in the survey group and in the control group. Within the other roentgenographic groups the control cases received rather more pneumothorax than did the survey cases. Despite this, satisfactory collapse was more common in the survey cases.

Thoracoplasty was performed in relatively few cases and its frequency was similar in both series. Pulmonary resection was seldom used, and in this material resection was first undertaken in the fifth year of observation.

Complications followed 36 per cent of the active measures in the survey series and 50 per cent of those in the control series.

In the *clinical analysis of results* after 8, 9 and 10 years the cases detected by mass radiography and the control cases were presented as undivided series. This permitted a good general view of the importance of the mass survey as a complement to the routine antituberculosis work in Södermanland County.

Most attention was devoted to the results after 8 years, since in all cases at least 8 years elapsed between diagnosis and follow-up. At the end of this time, 63 per cent of the survey cases and 48 per cent of the control cases remained on the register of tuberculous persons. Dead of pulmonary tuberculosis were 12 per cent of the survey series and 29 per cent of the control series. Deaths from other causes amounted to c. 5 per cent in both series. Removed from the register because of healing of tuberculosis were 19 per cent of the survey cases and 17 per cent of the controls. The difference in tuberculosis mortality (statistically highly significant) thus was the cause of the difference in the frequency of cases still registered.

Results satisfactory from the medical aspect, viz., healed, inactive or probably inactive tuberculosis were present after 8 years in 63 per cent of the survey series and in 50 per cent of the controls (statistically significant difference). Satisfactory "economic" results after 8 years were found

in 78 per cent of the survey series and in 60 per cent of the control cases (highly significant difference); the criteria for satisfactory results were removal from the register as cured or, if still registered, fit for full-time or part-time work, or unfit for work but not because of tuberculosis or its sequelae, or of pensionable age but with inactive or probably inactive tuberculosis. In the cases which could be followed up for 9 or 10 years, the changes in status from the respective preceding years were on the whole similar in the survey cases and in the controls.

In the *statistical analysis of results* the principal prognostic factors — roentgenographic extent of tuberculosis, E. S. R. and age at diagnosis — which were selected in accordance with the method described in chapter VIII, were first studied with respect to their effects in the combined mass survey and control material. Because the prognosis of pulmonary tuberculosis varies according to time and population, it was necessary to elucidate the guiding rules for this particular material.

Prognosis was studied as regards frequency of unfavourable results: 1) total unfavourable prognosis (tuberculosis still active or unstable at the end of 8 years or fatal during that period), 2) deaths from pulmonary tuberculosis during the 8 years, and 3) deaths from pulmonary tuberculosis within 1 year of diagnosis. The most unfavourable prognostic factors, far advanced tuberculosis and highly elevated E. S. R., were more common among the control cases than in the survey series. Age had somewhat less importance for prognosis, but with increasing age the prognosis on the whole was poorer. Since the average age of the survey cases was higher than that of the control cases, the age factor, in contrast to roentgenographic status and E. S. R., operated unfavourably for the survey cases.

Comparisons were made between control cases and survey cases with and without homogenization for the prognostic factors. These comparisons were based on the complete series and on their component roentgenographic groups.

Between the complete control material and the complete survey material the only significant difference *after homogenization* concerned mortality during the first year after diagnosis, which was greater in the control cases. Otherwise there were only tendencies to poorer prognosis in the control material.

The comparisons between the homogenized roentgenographic groups showed that the difference in first year mortality between the total series was chiefly due to significantly higher death rate in the far advanced controls. Of the other differences, almost all denoted tendencies to better prognosis for the survey cases. No significance was found, however, except as regards total unfavourable prognosis in moderately advanced tubercu-

losis, where the difference in favour of the survey cases was almost significant.

In fully homogenized material the method of diagnosis should not by itself influence prognosis. The differences which appeared in this investigation must be regarded as chiefly due to the variations which, despite the homogenization used, occurred within each roentgenographic group, mainly as regards extent of tuberculosis, but also in the E. S. R. and age groups. The significant difference in first year mortality between far advanced control cases and far advanced survey cases could be explained by the particularly wide roentgenographic variations permissible within this definition. The almost significant difference between the moderately advanced groups' total unfavourable prognosis seemed, from special study of the basic data, to be attributable to chance.

Comparisons between *heterogeneous* groups showed almost without exception greater differences than in homogenized material.

Tuberculosis without demonstrated activity initially or later

Of the registered cases in which the retrospective review failed to find definite tuberculous activity at diagnosis or later, those classed as *inactive* constituted 21 per cent of all the registered mass survey cases and 5 per cent of all controls. In the groups *probably active* and *probably inactive,* which together comprised 22 per cent of the survey series and 9 per cent of the controls, approximately one-third of the patients died of other causes than pulmonary tuberculosis. In most of these cases the fatal outcome curtailed the observation period to less than that stipulated for classification as inactive. The natural preponderance of survey-detected cases among those without activity was accentuated by the fact that the 1946 to 1948 survey was the first county-wide investigation in Södermanland. As mentioned, many of these cases were in the older age groups, which also explains the high death rates from nontuberculous causes.

Tuberculosis initially not active, later active

These "later active" cases constituted 7 per cent of all the registered survey cases and 1.5 per cent of all the controls. The risk of relapse within 8 years of diagnosis in all registered cases with inactive or probably inactive tuberculosis was 8 per cent in the combined mass survey and control series. The corresponding figure after the end of the fifth year was

4 per cent. These cases emphasize the difficulties of judging the prognosis in individual cases and the importance of keeping suspected cases under adequately long supervision.

CHAPTER X

Mental illness or mental deficiency was present in 8 per cent of the total mass survey series of registered cases and in 3 per cent of the total control series. Of the cases with mental complications, 66 per cent in the survey group and all in the control group had active tuberculosis at diagnosis. Among such active cases from the mass survey, far advanced tuberculosis was more common than among the total of active survey cases. The difference was statistically significant in the female patients but not in the males. Also mortality from pulmonary tuberculosis was greater among the mentally ill or deficient than among the total of active cases in the same series. The difference between the female groups was highly significant, but that between the male groups was not significant. The former difference therefore was associated with greater frequency of far advanced tuberculosis at diagnosis.

The poorer prognosis of pulmonary tuberculosis in mentally ill or deficient persons as compared with the general tuberculous population could thus be ascribed to more advanced lesions when the cases were first seen.

CHAPTER XI

In the cases from the mass survey which were placed under observation without being registered, the lesions either were only suspected to be tuberculous, or were regarded as healed tuberculosis which for various reasons nevertheless required supervision. These non-notifiable cases comprised 136 males and 139 females. Such cases, of course, also occur in the routine work of the tuberculosis dispensary. It would therefore have been misleading to have included the 275 in the comparison between registered mass survey and control cases. The retrospective evaluation, however, showed that 12 of the nonregistered survey cases had, in fact, active tuberculosis at diagnosis; in 9 cases the lesions were minimal. Like the registered cases, the nonregistered included a group with tuberculosis which was not active at diagnosis but became active later. This group contained 21 cases. The pulmonary lesions were found to be nontuberculous in 43 cases. In the remaining 199 cases the retrospective evaluation showed healed tuberculosis.

The cases of pulmonary tuberculosis found by two mass radiographic surveys of Södermanland County were compared. The first of these surveys *(MR I)* took place between 1946 and 1948, and the second *(MR II)* between 1953 and 1955. Of the population aged 7 years or over, 96.7 per cent were examined in MR I and 96.8 per cent in MR II.

At MR I 339 cases of active pulmonary tuberculosis, comprising 1.9 per thousand of the examined population, were notified. The corresponding figures in MR II were 204 and 1.1 per thousand.

The cases were grouped according to a modification of the NTA classification of tuberculosis. It was then found that advanced tuberculosis was more frequent in the series detected by MR I than in the MR II group. Thus, of the former cases 17.1 per cent had far advanced lesions, but of the latter only 8.3 per cent showed such disease.

The male/female distribution was almost equal in the active cases from both surveys. From MR I to MR II there was a pronounced shift towards higher ages in the male patients.

Tubercle bacilli were more often found by direct microscopy of sputum in MR I than in MR II. The total of positive bacteriologic tests, on the other hand, was higher in MR II. This was attributed mainly to increased frequency of gastric lavage.

All the cases of active tuberculosis discovered by MR II could be followed up for 2 ½ years and 130 were observed for 3 to 4 years. Deaths from pulmonary tuberculosis amounted to 0.5 per cent of the MR II cases after 2 ½ years and 1.5 per cent after 3 to 4 years. The corresponding mortality rates for the active cases from MR I were 8.0 and 10.7 per cent. The frequency of cavitary progression of the pulmonary lesions was also lower in the series from MR II.

These divergent frequencies may be presumed to reflect the changes which have occurred in the general tuberculosis situation in Södermanland County between the surveys. The radical changes as regards therapy were likewise evident. In the MR II series of active tuberculosis artificial pneumothorax and thoracoplasty were less extensively employed than after MR I, but specific drugs were more frequently given, and pulmonary resection was also used.

CONCLUSIONS

As regards pulmonary tuberculosis, community-wide mass radiography constitutes by its nature a rapid cataloguing of previously unknown cases within the region studied. Regardless of the survey's total duration, the time allowed each person to present himself for examination usually is limited to a few days. The large number of fresh cases of pulmonary tuberculosis which were detected by the mass survey of Södermanland County from 1946 to 1948 showed how necessary this investigation was.

The main object of mass radiography is to reveal pulmonary tuberculosis early in its course and thereby to curtail the time required for cure and by large improve the outlook for the individual patients. The investigation herein presented showed that the earlier detection of active tuberculosis by mass radiography resulted in substantial improvement of prognosis as compared with the outlook for active tuberculosis diagnosed by routine measures.

Another important aim of mass radiography is to disclose previously unknown sources of infection. In this respect, too, the Södermanland survey must be considered to have been highly successful.

In addition to tuberculosis, mass radiography of the chest is a useful means of discovering other pathologic conditions, such as tumours and cardiac disease. Findings of this type from the Södermanland survey were not within the scope of my investigation.

The second mass radiographic survey of Södermanland, from 1953 to 1955, reflected the considerable improvements which for many reasons have occurred in the tuberculosis situation. It also demonstrated, however, that the time is not yet ripe for cessation of county-wide mass radiography.

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Viikari, Sauli, docent, med fru, Turku
Virtanen, Ilmari, dr., med fru, Seinäjoki
Virtanen, Simo, dr., Turku
Wuorinen, Antero, överläkare, med fru, Oulainen
Wäre-Niskanen, Maija, dr., Helsinki
Yrjövuori, Paavo, överläkare, med fru, Kuusankoski

MINUTES OF THE PROCEEDINGS

Thursday, August 7th, 1 p.m.

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* published in these proceedings.

Section II

Friday, August 8th, 9 a.m.—12 a.m.

Dr. K. Isager took the chair.
Main Topic of the Discussion:

REHABILITATION OF TUBERCULOUS PATIENTS.

Section III

Friday, August 8th, 2 p.m.—5 p.m.

Dr. K. Rogstad took the chair.

Section IV

Saturday, August 9th, 10 a.m.—1 p.m.

Prof. E. Hedvall took the chair.

SOCIAL PROGRAM

On August 7th the members of the Congress were the guests of the City of Turku in the Concert Hall. On August 8th the ladies visited Kalevanniemi Sanatorium and the summer residence of the President of Finland, and in the evening a banquet was held at the Casino in the town of Naantali. On August 9th a luncheon was given by the Finnish Society for Prevention of Tuberculosis. A post-congress tour was made to Central Finland.

AN DER WEGSCHEIDE: TUBEKULOSEBEKÄMPFUNG ODER BEKÄMPFUNG VON LUNGENKRANKHEITEN UNSERE AUFGABE IN DER ZUKUNFT?

Von

Erik Hedvall [1]

Die Bekämpfung der Tuberkulose ist nun mit einem so bedeutenden Erfolg fortgeschritten, dass es notwendig ist, ernsthaft unsere Aufgabe in der Zukunft zu erwägen. Nicht dass wir Ärzte "brotlos" zu gehen brauchen, solche und ähnliche Probleme lösen sich immer in einer Welt, die mit Krankheiten und Not angefüllt ist, sondern wir müssen erwägen, und nochmals erwägen, wie unsere in den Jahren erworbene Erfahrung auf die für alle am besten und meist zufriedenstellende Art angewandt werden kann. Diese Frage war schon früher das Ziel von Diskussionen an verschiedenen Stellen, unter anderem in der Schwedischen Lungenärztevereinigung (Svenska Lungläkarföreningen). Sie erscheint mir jedoch so wichtig, dass ich vorschlagen möchte, sie als Hauptthema, auch auf einem nordischen Tuberkulosekongress, aufzunehmen. Das Anliegen könnte dort passend von den Representanten der verschiedenen nordischen Länder beleuchtet werden, und die Frage — wenn möglich — gelöst, wenn auch nicht auf eine einheitliche, so doch eventuell auf eine für jedes Land passende Weise.

Dei Tuberkulose-*sterblichkeit* in Schweden beträgt jetzt nur noch 8 auf 100.000 Einwohner im Jahr und sinkt weiter. Die Kindersterblichkeit ist beinahe vollkommen verschwunden. Auch die totale Tuberkulosesterblichkeit hat so niedrige Ziffern erreicht, dass man überlegen kann, ob man länger Nutzen davon hat, sie für jede Provinz gesondert zu registrieren, oder ob es nicht z.B. besser wäre, die Zahlen für Götaland, Svealand und Norrland jeweils zusammen zu nehmen. Die sinkende Sterblichkeit wäre dann leichter abzulesen. Die Gesamtzahl der an Tuberkulose erkrankten (alle Formen von Tuberkulose) in Schweden ist in 10 Jahren von 86.938 auf 65.031 gesunken, also mit ca 25 %. Gewisse Formen von Tuberkulose, welche früher so verbreitet waren, wie auch die Kindertuberkulose, sind nun beinahe vollkommen verschwunden, und die Ansteckungsquellen wie auch die Tuberkuloserezidive sind an Zahl zurück-

[1] Lungenklinik, Uppsala, Sweden.

gegangen. Alles dieses hat natürlich den Bedarf an Pflegeplätzen stark beeinflusst. Einige Sanatorien, z.B. Spenshult und Hålahult, sind vollkommen für andere Zwecke in Gebrauch genommen worden. Hässleby Sanatorium ist jetzt für tuberkulöse Alkoholiker eingerichtet worden. Der Zwangsaufenthalt dort heilt wohl nicht für immer die Patienten von ihrem Alkoholismus, aber er garantiert ihnen eine ausreichend lange Pflege für ihre Lungenkrankheit, etwas was man früher selten durchführen konnte. Viele B-Sanatorien sind niedergelegt, oder für andere Zwecke in Gebrauch genommen worden. Überall im Lande stehen viele Plätze in unseren Sanatorien leer. Obwohl eine recht grosse Anzahl Plätze für nicht tuberkulöse Lungenfälle, für chronische Pflegefälle und so weiter angewandt werden, waren im Jahre 1957 nicht weniger als 2.119 von 6.847 Plätzen unbelegt in Schweden. (Im Jahre 1956 war die entsprechende Zahl 1.620 von 7.329). Für das ganze Land gilt ausserdem, dass die unsichere Zukunft auf dem Gebiet der Tuberkulose es schwer macht, Bewerber für Unterartzstellen zu bekommen, oder Vertreter für diese zu beschaffen. Entsprechende Verhältnisse machen sich mehr oder weniger in allen nordischen Ländern geltend. Der Zeitpunkt für eine ernsthafte Überlegung, wie wir es auf die beste Art für die Zukunft ordnen sollen, dürfte also gekommen sein.

Als diese Frage im vorigen Jahre durch die Lungenärztevereinigung (Lungläkareföreningen) auf der Schwedischen Ärztegesellschaft in Stockholm zur Diskussion aufgenommen wurde, äusserte der Chef der Schwedischen Medizinalbehörde, Generaldirektor Dr. Med. *Engel,* folgendes (zit. Nordisk Medicin 1957(57) :560) :

"Generaldirektor *Engel* hob in der Diskussion hervor, dass es im Hinblick auf die sinkende Tuberkulosemorbidität notwendig wäre, ohne Zeitverlust ein genaues Programm für die Organisation der Tuberkulosepflege in der Zukunft vorzulegen. Nicht zuletzt mit Rücksicht auf den Nachwuchs von Spezialisten auf dem Gebiet der Lungenkrankheiten wäre eine solche Massnahme erforderlich. Er legte weiter zur Begründung einen Entwurf über die Organisation der Krankenhausbehandlung von Lungenkranken vor. In jeder der geplanten sechs Krankenpflegezonen im Reich sollte eine besondere Thoraxklinik eingerichtet werden, worin ein auf Lungenkrankheiten spezialisierter Internist mit eingehen soll. In den untergeordneten Krankenpflegebezirken, das heisst die Regierungsbezirke und die freien Städte, sollte man danach streben, ein Sanatorium zu einem Krankenhaus für Lungenkrankheiten im Allgemeinen einzurichten, eine Lungenklinik also, und diese sollte die engste Zusammenarbeit mit dem Zentralkrankenhaus pflegen. Engel hob weiter hervor, dass die Bautätigkeit auf dem Gebiet der Krankenpflege zur Zeit stark gehemmt ist und dass man während einer langen Übergangszeit damit rechnen müsste, die

Sanatorien, welche einigermassen leicht mit dem Krankenhaus in Verbindung stehen können, beizubehalten und als Lungenkliniken arbeiten zu lassen.

In der Frage der poliklinischen Tuberkulosefürsorge legte Engel seine Ansicht dar, dass die Distrikts-Dispensärsprechstunden niedergelegt werden könnten während die Dispensärschwestern beibehalten werden müssten. Auch die Zentraldispensäre sollten bestehen bleiben, doch wird deren Arbeit erweitert in Übereinstimmung mit dem, was oben für die zukünftige Tätigkeit der Sanatorien aufgezeichnet worden ist."

Die Gesichtspunkte, die eben für das Bedürfnis an Lungenkrankenpflege und ihre zukünftige Organisation angeführt worden sind, haben eine Überprüfung der Tätigkeit an der Uppsala-Klinik notwendig gemacht. Die Spezialistausbildung, die bisher hier mit dem Schwerpunkt auf der Tuberkulose betrieben wurde, ist nicht mehr ausreichend und muss bedeutend erweitert werden. Das Ziel muss sein, Lungenspezialisten auszu-
an den neuen Lungenabteilungen in den Zentralkrankenhäusern zu über-
bilden (nicht nur Tuberkuloseärzte), die in der Lage sind, die Leitung

Den Lungenkliniken darf darum nicht nur die Ausbildung in Tuberkulose überlassen werden, sondern sie muss eine solche ebenfalls geben in Bronchoskopie, Bronchographie, Tomographie, Klinische Physiologie, Cytologie und im gewissen Umfange auch in Bakteriologie und Tierversuchen, Asthmatestung, Provokationsversuch u.s.w. Es ist nicht ausreichend, dass diese Untersuchungen an anderen Teilen des Akademischen Krankenhauses ausgeführt werden. Die Unterärzte müssen die Untersuchungen selbst vornehmen, um das Gebiet beherrschen zu können, wenn sie an einem anderen Platz in verantwortliche Stellung kommen. Die Umorganisation darf jedoch nicht auf die Weise vor sich gehen, dass die Ausbildung auf anderen Spezialgebieten verschlechtert wird. Diese Frage ist darum hauptsächlich mit Vertretern der Hals-Nasen-Ohrenklinik und der zentralen Röntgenabteilung des Akademischen Krankenhauses diskutiert worden. Man konnte sich darüber einigen, das Patientenmaterial so zu verteilen, dass die verschiedenen Kliniken, die werdenden Lungenspezialisten, und die Patienten bei dieser Entwicklung nur gewinnen können.

Seitdem dieses klar wurde, habe ich bei den medizinischen Fakultäten und Direktionen eine Eingabe über die Aufrüstung der Lungenklinik gemacht, welche man kurz in folgenden Punkten zusammenfassen kann. Es kann jedoch nicht genug unterstrichen werden, dass man es hier nur mit einem Vorschlag zu tun hat. Auch wenn alle im Augenblick an einer Lösung im Sinne dieses Vorschlages interessiert zu sein scheinen, so weiss man bisher doch noch nicht, ob diese Pläne sich realisieren lassen. In Hinblick auf die Entwicklung auf dem Gebiet der Tuberkulose sehe ich es jedoch für richtig an, schon jetzt über den Inhalt des Vorschlages zu spre-

chen, und dieses deshalb desto mehr, weil gleichartige Probleme sich sicherlich an anderer Stelle geltend machen.

1. Eine der drei Krankenabteilungen an der Lungenklinik wird teilweise zur Untersuchungs- und Forschungsabteilung umgestaltet. Dorthin wird der Operationssaal und die Röntgenabteilung überführt, welche zur Zeit im Zentraldispensär gelegen sind. Weiter wird die Abteilung mit Apparaten für Tomographie, Bronchoskopie und Bronchographie ausgerüstet. Ein Raum ist für klinische Physiologie gedacht (nur für Tuberkulosepatienten).

2. Dem Akademischen Krankenhaus ist eine Professur für klinische Physiologie bewilligt worden. Der Inhaber dieser Professur soll nicht nur der Chef seiner eigenen Abteilung sein, sondern auch an der dafür bestimmten Abteilung der Lungenklinik. Davon wird enge und fruchtbare Zusammenarbeit mit dem genannten Professor und den Ärzten der Lungenklinik erwartet.

3. *Die Bronchoskopie* soll an der Lungenklinik nur an Tuberkulosepatienten durchgeführt werden (von der Lungen- und Thoraxchirurgischen Klinik), alle übrigen Patienten sollen an der Hals-, Nasen- und Ohrenklinik untersucht werden. Dadurch wird die Tuberkuloseansteckungsgefahr von der letzgenannten Klinik ferngehalten. Damit die Untersuchungsresultate nicht an Wert verlieren sollen, wird die Bronchoskopie unter der Leitung von Ärzten der Hals-Nasen-Ohrenklinik ausgeführt. Die Unterärzte der Lungenklinik sollen assistieren und allmählich selbst die Eingriffe ausführen dürfen.

4. *Die Bronchographien* werden nach dem gleichen Prinzip organisiert wie die Bronchoskopien.

5. *Die Tomografie* wird in der Lungenklinik ausgeführt, sowohl an sämtlichen dort liegenden Fällen wie auch an den Besuchern des Zentraldispensärs, bei denen eine solche Untersuchung notwendig ist. Alle übrigen Untersuchungen dieser Art finden in der zentralen Röntgenabteilung statt.

6. Ab sofort wird die Klinik für *Cytologie, Bakteriologie, Tierversuche, Asthmateste* usw. eingerichtet.

7. Eine Eingabe über die Umwandlung meiner persönlichen Professur in Phthisiologie in eine Professur für Lungenkrankheiten ist gemacht worden.

8. Die Umorganisation bringt auch für die Unterrichtung der Studenten und für die Forschung grössere Möglichkeiten mit sich.

Damit bin ich am Schluss meines kurzen Berichtes über die Pläne, welche wir für den Ausbau und die zukünftige Tätigkeit an der Lungenklinik hegen. Es dürfte wohl kein Zweifel darüber bestehen, dass dieser Vorschlag einen Schritt in der rechten Richtung darstellt. Ob er realisiert werden kann, wird die Zukunft zeigen.

FROM THE DEPARTMENT OF PULMONARY DISEASES,
ST. GÖRAN'S HOSPITAL, STOCKHOLM, SWEDEN,
CHIEF: SVEN LÖFGREN, M.D.

DEFINITION AND DIAGNOSTIC CRITERIA OF SARCOIDOSIS

By

SVEN LÖFGREN

It is a generally accepted opinion that the sarcoidotic tissue reaction is a cornerstone where the diagnostic delimitation of sarcoidosis is concerned. Here I shall refrain from more closely discussing histopathologic details, but I wish to emphasise the well-known fact that essentially the tissue reaction associated with sarcoidosis is rather nondescript. Similar changes are thus to be found in bacterial infections such as tuberculosis and leprosy, in tertiary syphilis, in fungous infections such as coccidioidomycosis, histoplasmosis and moniliasis, as well as in lesions due to the presence of foreign bodies, among which conditions berylliosis and silicosis should be mentioned in the first place.

The aetiology being obscure, and the histopathologic lesions which provide the basis for the variable clinical symptoms being non-specific in type, it is obviously a perplexing task to define the concept of sarcoidosis. None the less, when we meet in this symposium we know exactly what disease we are going to discuss, and there would seem to be rather little danger of misunderstandings. Certainly our theoretical discussions may engender considerable disagreement, but in our practical activities, in clinical work with diagnosis and treatment, presumably we are acting on fairly uniform lines.

With this I have already intimated that from the practical point of view I regard the clinical criteria as constituting the diagnosis of sarcoidosis. In all instances including those clinically typical, naturally we are bound to seek conformation by biopsy of our clinical diagnosis. Especially in the cases that are clinically obscure or doubtful, our task is twofold, viz., partly by the means available to rule out other conditions which might have to be considered — tuberculosis, mycosis, pneumonoconiosis — and partly by biopsy possibly to corroborate a diagnosis of suspected sarcoidosis. However, if in a case where I have found clinical and histopathologic criteria of sarcoidosis I should happen to demonstrate tubercle bacilli,

I would not for this reason necessarily change my diagnosis from sarcoidosis to tuberculosis. I have seen several patients who in my opinion had both diseases at once. This interpretation does not appear to me more unreasonable than the simultaneous diagnosis in one patient of tuberculosis and syphilis, or tuberculosis and streptococcal infection, or tuberculosis and silicosis.

Reverting to the relationship between histopathologic and clinical criteria in sarcoidosis, I should like to formulate my opinion in the following manner. When we gather together all those conditions associated with a sarcoidotic tissue reaction of known aetiology, viz., tuberculosis, leprosy, tertiary syphilis, fungous infections, and certain foreign-body reactions, all these conditions together form a minority, which besides has a very variable clinical picture. When we consider the large majority of cases with sarcoidotic lesions we find that the aetiology is unknown, and this group with unknown aetiology presents plenty of clinical features common to many cases, which together all but mark the disease as a clinical entity.

Having said this I feel bound to state briefly the clinical criteria upon which I base the diagnosis of sarcoidosis. Even the age distribution is peculiar, since unlike tuberculosis the syndrome with few exceptions does not occur before the age of twenty.

No clinical symptom can alone be considered pathognomonic for sarcoidosis. We must always reckon with a constellation of characteristic symptoms which give us the diagnosis. For the time being, in my opinion the pulmonary involvement in this respect should be regarded as essential within the clinical picture. We may certainly observe local sarcoidotic structures in single organs, for example in a removed cervical lymph node. If otherwise a characteristic clinical picture of sarcoidosis is lacking, so far I feel disinclined or in doubt to refer the case to sarcoidosis.

As in the case of tuberculosis, also in sarcoidosis it is important to distinguish between the early and the chronic stage. The most characteristic picture no doubt is that of the early stage of sarcoidosis.

The clinical criteria of early or primary sarcoidosis I prefer to formulate as follows. Most typical are the large bilateral, comparatively symmetric, polycyclic hilar lymphomas, in about one-third of the cases associated with paratracheal glandular enlargement, usually on the right side. Characteristic is the relative anergy to tuberculin and other bacterial allergens. In most cases of primary pulmonary sarcoidosis there are no subjective or systemic symptoms, and the disease therefore is apt to remain hidden unless the patient undergoes routine chest X-ray. In certain instances, especially in women, early sarcoidosis is announced by erythema nodosum. Here lactation seems to act as a provoking factor, presumably through hormonal influences. In such a case the picture usually is com-

plicated by fever, articular symptoms and elevated erythrocyte sedimentation rate. In about 40 per cent shotty or patchy parenchymal densities are noted, as a rule not until the hilar lymphomas have begun to diminish. The prognosis of primary pulmonary sarcoidosis is decidedly favourable: in more than 90 per cent hilar lymphomas as well possibly supervening parenchymal lesions subside within a year or two.

In the presence of pronounced symptoms, and especially of large hilar lymphomas, the clinical picture of primary sarcoidosis will scarcely give rise to confusion with other morbid conditions. The disease that as regards x-ray findings most closely resembles primary sarcoidosis would seem to be coccidioidomycosis. This condition, however, only occurs in certain geographical regions. If the lymphomas are smaller, tuberculosis plays the principal part in differential diagnosis.

The pulmonary lesions of the chronic stage, patchy densities, fibrosis, and emphysema, are far less helpful in diagnosis than the lesions of early sarcoidosis. Differentiation from tuberculosis, fungous infections, and pneumonoconiosis will sometimes be difficult.

When the pulmonary lesions — as in the chronic stage — are nondescript we must instead have recourse to the frequently present extrapulmonary changes, several of which are nearly pathognomonic in character. Here I have in mind uveoparotitis, typical sarcoids of mucosae and skin, in particular scar sarcoids, and osseous metastases. Among abnormal findings in the field of blood chemistry we note in the active, generalising stage hyperglobulinaemia, often an increase of uric acid in the blood, and occasionally — in conjunction with hypercalcaemia — a peculiar disturbance of renal function.

In the foregoing I have tried to outline the clinical criteria by which I am guided in making a diagnosis of sarcoidosis, and I wish to emphasise once more that naturally it is desirable to substantiate the diagnosis by means of biopsy. The characterisation given does not claim to be a precise or final definition of the sarcoidosis concept; in my opinion this is an impossibility while the aetiologic factor or factors remain obscure. It furnishes a provisional but very useful frame for the clinical work. To the extent that new findings of aetiologic importance will be obtained these may necessitate adjustment and probably extension of the limits proposed. Conceivably certain cases now considered typical will be discarded, but probably or possibly in the future — through demonstration of an infective agent — still more cases, which at present are regarded as uncharacteristic and uncertain, will have to be included in the sarcoidosis group.

DISCUSSION

L.-E. Warfvinge, Sweden:

When discussing the aetiological possibilities in sarcoidosis, it might be of interest to mention the studies of Xalabarder which have recently been published in Spanish medical journals. This author suggests that the asteroid bodies which are found in some giant cells from sarcoid foci, and which are considered characteristic of the disease, may well be one of the intermediate forms encountered in the normal development of *Mycobacteria.*

These intermediate forms of reproduction which are neither bacillary nor acid-fast, the author inoculated into guinea-pigs. The histological lesions that developed were very similar to those of sarcoidosis and, what is more astonishing, most of the guinea-pigs remained insensitive to tuberculin tests!

Ingrid Gilg, Denmark:

What examinations are necessary to distinguish whether a case should be excluded from or considered to be sarcoidosis?

At the Dermatological Department of the Finsen Institute in Copenhagen, all patients with sarcoidosis or with a suspected diagnosis of this disease are examined according to a given systematic plan, which includes numerous special examinations.

FROM THE DEPARTMENT OF PULMONARY DISEASES,
ST. GÖRAN'S HOSPITAL, STOCKHOLM, SWEDEN,
CHIEF: SVEN LÖFGREN, M.D.

IMMUNOLOGICAL AND AETIOLOGICAL ASPECTS OF SARCOIDOSIS

By

SVEN LÖFGREN

When we speak of immunological data in connection with sarcoidosis we are largely "up in the air", because nothing is known of the aetiology of the disease. If the syndrome is caused by an infection, which I think it is, we do not know anything of the nature of the supposed infective agent. Instead, the immunological data such as discussed by us pertain essentially to the relation to tuberculosis.

The relation of sarcoidosis to tuberculosis is an old controversial question, and we can scarcely refrain from touching upon it also in this connection. The arguments advanced in support of the opinion that sarcoidosis is a special form of tuberculosis are probably above all the following:

1. A certain resemblance of the histopathologic pictures;

2. The fact that in a minor proportion of cases of sarcoidosis demonstration of tubercle bacilli has been successful;

3. Further, it has been argued that the relative anergy to tuberculin would seem to suggest that sarcoidosis is a tuberculous condition, viz., strictly speaking, tuberculosis in subjects with an extraordinarily high power of resistance against infection with tuberculosis. The weak or negative reaction to tuberculin has been taken to indicate a so-called positive anergy;

4. The most important argument for sarcoidosis being a form of tuberculosis is the fact that classical tuberculosis supervenes during the later course of sarcoidosis in a not quite insignificant number of cases and that some patients die of tuberculosis. A somewhat closer discussion of this important point seems to be of some interest.

Reports of the development of tuberculosis in the later course of sarcoidosis were especially numerous in the older literature. It should be pointed out in this connection that the major proportion of these patients with sarcoidosis were treated in sanatoria and hence obviously exposed to tuberculous infection. Of recent years there has been a considerable ad-

vance in the diagnosis of sarcoidosis, and it happens much less often that a sarcoidosis patient is admitted to a sanatorium together with patients suffering from infectious tuberculosis. Correspondingly also the reports on supervening tuberculosis in cases of sarcoidosis have become less frequent. More recent investigations by Björnstad in Norway and Törnell in Sweden have disclosed that the occurrence of tuberculosis and sarcoidosis in one and the same patient is comparatively rare, and is scarcely more frequent than is to be expected on statistical grounds.

If also sarcoidosis cases would show an over-morbidity and over-lethality of tuberculosis, this would not necessarily be more remarkable than the well-known fact that patients with silicosis comparatively often develop tuberculosis and die of this disease; for this reason nobody has ever drawn the conclusion that silicosis were a special form of tuberculosis. Provided that sarcoidosis is a clinical entity unconnected with tuberculosis, the opinion might certainly be maintained that in the two diseases silicosis and sarcoidosis a lowered resistance to tuberculous infection might reasonably be expected, owing, perhaps, to the marked impairment of the lymphatic system.

In those instances where sarcoidosis and tuberculosis in any of their stages occur in one and the same subject, three possibilities are theoretically conceivable:

1. Sarcoidosis precedes the development of tuberculosis, i.e., precisely the sequence of events which is well known from the literature and which we just have discussed.

2. Tuberculosis develops prior to the onset of sarcoidosis; this is admittedly less well known from the literature, but actually much more common than the above sequence. Evidence to this effect is already the simple fact that formerly the tuberculous primary infection took place most frequently during childhood, whereas sarcoidosis as a rule is not observed before the age of twenty. In instances of primary pulmonary sarcoidosis it is noted that about 50 per cent of the patients are tuberculin-positive, which indicates a preceding tuberculous infection. In many of these tuberculin-positive patients, also criteria other than the response to tuberculin are found as to a preceding tuberculous infection, e.g., chest X-rays showing calcification, or a clinical history of pleurisy or pulmonary tuberculosis.

Sarcoidosis may thus be followed by tuberculosis; it is still more common, as I have just stated, that tuberculous infection precedes the development of sarcoidosis.

3. The third possibility is that both diseases are present at the same time, and cases of this type claim the greatest interest in the discussion of the relation between tuberculosis and sarcoidosis. I have seen several of these cases and propose briefly to report on one of them.

The patient was a woman aged 20 with bilateral hilar lymphomas, in appearance typical of sarcoidosis. Mantoux, 100 units, was negative. Scalene node biopsy disclosed the features of sarcoidosis. The patient was referred to a convalescent home for tuberculous patients, which undoubtedly was rather inappropriate; there was thus the possibility of tuberculous infection. When retested after six months the patient was tuberculin-positive. The hilar lymphomas had shrunk, but instead there was an infiltration in the lower lobe of one of the lungs; subsequently bilateral lesions developed with a cavity on one side, and acid-fast rods pathogenic to the guinea-pig were demonstrated in the sputum. The classical tuberculosis had thus developed in this patient who some months previously had shown a fully typical picture of early sarcoidosis. The interesting observation in this case was that a cicatricial sarcoid developed at the site of the lymph node biopsy while the tuberculosis was in full activity. The scar displayed oedema and yellowish-red discolouration, and a biopsy specimen showed typical sarcoidotic changes. Hence, in this patient there was simultaneous activity of sarcoidosis as well as of tuberculosis. To me this fact seems definitely to discourage the opinion that sarcoidosis, on account of some kind of an immune-biological turn-over, would merge into classical tuberculosis, and instead to encourage the opinion that the two diseases are independent of each other.

I shall now proceed to mention some further arguments supporting the opinion that sarcoidosis is an independent disease unconnected with tuberculosis.

1. The sarcoidotic lesions often affect organs where tuberculous changes are rarely found, e.g., salivary glands, the eyes, and striated muscles. On the other hand, they scarcely occur in certain other structures where tuberculosis is not infrequently observed, e.g., meninges and adrenals;

2. The difference in age distribution between the two diseases I have already mentioned. Whereas tuberculosis, at least formerly, was common in childhood, sarcoidosis with few exceptions does not occur until the age of twenty;

3. Whereas the morbidity and mortality of tuberculosis are rapidly decreasing in large parts of the civilised world, the incidence of sarcoidosis is not decreasing but possibly rising;

4. The response to treatment is essentially different in the two diseases. The antibacterial therapy of tuberculosis (streptomycin, PAS, INH, Conteben) is unsuccessful in sarcoidosis. Treatment with ACTH and cortisone has a favourable action on sarcoidosis but, as is well known, may be dangerous in tuberculosis unless combined with the just mentioned antibacterial agents;

5. The Kveim test is positive in a high percentage of sarcoidosis cases but in very few cases of tuberculosis;

6. Every phthisiologist knows that to a certain degree tuberculosis is a social disease. Among the tuberculosis clientele chronic alcoholism, vagabondism, etc., occur to a remarkable extent. Thus, unfortunate social con-

ditions seem to favour the origination and development of tuberculosis. On the other hand, tuberculosis would seem to some extent to dispose towards asociality;

When surveying 400—500 sarcoidosis cases we were surprised to find that this disease by no means has the same connection with social disadvantages as tuberculosis. There are quite different factors that act predisposingly in sarcoidosis, e.g., hormonal influences. Without embarking on a detailed discussion of this aspect I wish merely to point out that the pathogenesis appears different in the two diseases;

7. As a seventh point I wish to state the phenomenon to which I personally attribute perhaps the greatest importance in the interpretation of the immune-biological relation between tuberculosis and sarcoidosis, i.e., the development of erythema nodosum in the early stages of both diseases.

According to the collected experience, erythema nodosum is to be regarded as a hyperergic symptom. Patients with primary tuberculosis and erythema nodosum respond, as is well known, very strongly to tuberculin, which indicates hyperergy to the tuberculous allergen. Early — so-called primary — sarcoidosis, with or without erythema nodosum, is evidently associated with relative *anergy* to tuberculin. If sarcoidosis, as is sometimes asserted, were an anergic form of tuberculosis, how then is it to be explained that it occurs conjointly with the *hyperergic* symptom, erythema nodosum?

DISCUSSION

L.-E. Warfvinge, Sweden:

The well known and diagnostically important tendency to extinction of the tuberculin reaction and other skin tests in sarcoidosis has been subject to many interpretations and has been considered proof against, as well as for, the tuberculous aetiology of the disease. This insensitivity to tuberculin is certainly different from that of a non-infected person and could be explained as a blockage of some of the functions of the reticulo-endothelial system. According to Scandinavian tuberculin examinations in sarcoidosis (Gravesen, Löfgren & Lundbäck), about 5 % of the cases are positive to 1 TU of OT, 35 % positive to 10 or 100 TU and 60 % negative to 100 TU. Lemming has proved that tuberculin-negative cases of sarcoidosis remain negative after BCG-vaccination.

Recently Pyke & Scadding published their observations of the tuberculin reaction in sarcoidosis under ACTH or cortisone treatment. They observed after 5—6 days' treatment an activation or sensitization in earlier negative cases. The same effect was noticed if a mixture of cortisone and tuberculin was injected locally. This increased sensitivity was transient in patients

tested repeatedly, even though corticosteroid therapy was continued. This phenomenon is strange, since ACTH and cortisone otherwise have a blocking effect on cutaneous reactions of the delayed type.

In Hällnäs Sanatorium we have since the summer of 1955 tested some 90 cases of sarcoidosis simultaneously with Old-Tuberculin and Endo-Tuberculin, the latter being a biologically highly active fraction extracted out of living tubercle bacilli, as described by Billaudelle and Warfvinge. The Endo-Tuberculin is rich in glycolipoids but contains very little protein, and, as Refvem has demonstrated the importance of the lipoid fraction of TB for the genesis of the epithelioid cell tubercles, it seemed of interest to compare the skin sensitivity in sarcoidosis to the two different tuberculins. In every single case the result was analogous: if the patient reacted to tuberculin, he reacted to both OT and ET; if insensitive, neither OT nor ET gave a reaction.

Alf Westergren, Sweden:

On some occasions, *i.a.* in discussions on the relationship between tuberculosis and sarcoidosis, I have called attention to a consideration which apparently has not received much attention; namely, the phenomenon called *alternating reactions* of the organism. In persons who have, or have had, tuberculosis it is fairly common to find chronic polyarthritis ("rheumatoid arthritis") or sarcoidosis as a second disease. Those who have the opportunity to follow up their patients over sufficiently long periods remarkably often find that an active phase of the tuberculosis subsides, to be replaced by active sarcoidosis *(or vice versa),* with a corresponding alternation in the tuberculin sensitivity. (A few such cases were reported about twenty years ago by Lemming.) I for my part have seen cases with up to three or four such alternating phases. Alternations similar to those between tuberculosis and sarcoidosis may also be observed between the former and chronic polyarthritis, as well as in other, less typical combinations.

In considering the etiology of an infectious disease we usually take only one type of micro-organism (bacterium or virus) into account; but if we are less rigid in the definition of "etiology" and also reach a point bordering on "pathogenesis", we very often have reason to reckon with a large number of factors, constant or variable, and not the least other infections of various types, with an unfavorable or perhaps sometimes a favorable effect. This, it seems to me, constitutes an explanation of the tendency to a cyclic course that may be found in a majority of "chronic" diseases; and with this mode of approach we may at least shed a little light, from a new aspect, on the undoubted enigma of the relationship between tuberculosis and sarcoidosis.

FROM THE DERMATOLOGICAL HOSPITAL, UNIVERSITY OF HELSINKI, FINLAND.
CHIEF: PROFESSOR TAUNO PUTKONEN, M.D.

THE KVEIM REACTION

By

TAUNO PUTKONEN

The etiology and pathogenesis of sarcoidosis (sarcoid of Boeck) are still obscure in spite of the fact that this disease has been the subject of scientific interest during several decades. It is also frequently difficult to establish the diagnosis on the basis of the clinical signs, x-ray and laboratory studies, and microscopic examination of biopsy specimens. For this reason attempts have been made to develop a diagnostic cutaneous test for this disease.

The first to report such a reaction were Williams & Nickerson [1], in 1935. They assumed that sarcoidosis was a virus disease, and prepared antigen from a cutaneous node of a sarcoidosis patient, in the same manner as Frei's antigen is prepared from the affected inguinal lymph nodes of patients with lymphogranuloma venereum. When the antigen was injected into four patients with sarcoidosis, a papule developed within 24 hours at the site of the injection in all of them, while four control patients failed to show such a reaction. The papules, however, disappeared in about a week, which — in the light of our present knowledge — indicates that the reaction was only a nonspecific irritation phenomenon.

The experiments reported in 1941 by the Norwegian Kveim [2] proved successful. He prepared his antigen from cutaneous nodes and enlarged lymph nodes of patients, much as the above investigators, and injected it into thirteen patients with sarcoidosis. A reddish brown papule appeared at the site of injection in twelve of these cases, but as late as one to four weeks after the injection. The papule showed the histological features of sarcoidosis. Control patients with skin tuberculosis and syphilis gave no reaction, nor did the sarcoidosis patients when injected with Frei's antigen. From this Kveim concluded that there was a question of a specific allergic reaction and not of a sarcoid type of reaction to nonspecific protein.

This peculiar late reaction, now known as the Kveim reaction, was two years later corroborated by Danbolt's [3] studies at the Dermatological

Clinic, Oslo, and by Putkonen's [4] studies at the Finsen Institute, Copenhagen. Positive reactions were obtained in all 10 sarcoidosis patients in the former series, and in 33 out of 42 patients, or 79 per cent, in the latter series. None of the control patients, totalling 16 in the former series and 65 in the latter, gave a definite positive reaction. Since then, several series of studies have been published in Scandinavia and the United States [5—12], covering a total of over 350 patients with sarcoidosis and nearly 500 controls. The incidence of positive reactions in these series varies from 73 to 96 per cent for the sarcoid patients, and from 0 to 7 per cent for the controls.

In Putkonen's series the Kveim reaction was positive in all of the 30 patients who showed cutaneous manifestations of sarcoidosis, but in none of the 8 patients whose cutaneous manifestations had already disappeared. From this finding Putkonen inferred that a positive Kveim reaction is a sign of active sarcoidosis which disappears with cure of the disease. This was later confirmed by Nelson [6, 7] and Rogers & Haserick [10]. It has even been observed that a Kveim reaction, after becoming negative during the clinical regression of the sarcoidosis, was reversed to positive when there was obvious clinical reactivation of the disease (Nelson & Schwimmer [12]).

There are reports, however, which seem to point against the specificity of this reaction. It should be noted in particular that Sones and Israel with co-workers [13, 14] obtained a positive Kveim reaction in sarcoidosis in only slightly over 20 per cent of the patients with sarcoidosis but in over 40 per cent of those with tuberculosis. Such results can no longer be accounted for by the fact that a series includes an exceptionally high proportion of cured sarcoidosis patients: the explanation must be sought elsewhere.

By comparing 32 antigens prepared from various tissues of different patients, Putkonen [4] showed that only some of these antigens were fully acceptable. He stated that some antigens give very strong nonspecific reactions which do not disappear until long after the injection. It is possible then to find epitheloid cells also in control patients. These reactions are misleading if the result is only read — as some investigators do — from a biopsy taken after a fixed interval, without following the development of the reaction. Other antigens, again, are so weak that the Kveim reaction only appears after several weeks. When these antigens are used, sarcoid patients with weak reactivity tend to be classified as negative if the observation time is not long enough. Few antigens are sufficiently strong to produce large, necrotic Kveim reactions. By suitably diluting these antigens, the most selective antigens causing no inflammatory early reactions are obtained. — Each new Kveim antigen should

be assayed carefully on both sarcoidosis and control patients before being used routinely. On this basis the criteria for a positive reaction should be determined for each individual antigen. Standardisation is out of the question, because the preparation of good Kveim antigens still offers so much difficulty.

Although the Kveim test, properly performed, is a valuable diagnostic aid, it is not specific in the sense that the source of active antigen would be limited to sarcoid tissue alone. This was demonstrated by Putkonen [4] with two antigens prepared (1) from enlarged lymph nodes of a patient with lymphatic leukemia, and (2) from tuberculous cervical lymph nodes. Both gave rise to typical though not very strong reactions in sarcoid patients, but not in control patients. Nelson [6, 7] prepared an antigen from normal spleen obtained at autopsy, and it proved equally selective as the Kveim antigen proper used by him. Though this observation was not reproducible in two later studies [8, 10], it must be borne in mind in further work on this problem. It is well known that not nearly all suspensions prepared from sarcoid tissue are acceptable antigens.

It has also been suggested that the Kveim reaction is caused by the killed tubercle bacilli contained in the antigen, or by their disintegration products. Starting from the fact that a typical sarcoid nodule had been produced in a sarcoidosis patient, in one case with BCG vaccine [15], and in another case with virulent human tubercle bacilli [16], Warfvinge [17] carried out an investigation using killed tubercle bacilli; in 5 patients with sarcoidosis a cutaneous reaction developed which was similar in development and in histological appearence to the type of reaction described by Kveim. In control patients with tuberculosis, however, there was only an early reaction which gradually decreased in size. Traces of this reaction were usually seen or at least palpated as long as one month after the injection. Histological examination showed nonspecific inflammation or smaller necroses surrounded by tuberculoid tissue. These observations were confirmed by Bjørnstad [18], and they were rendered even more interesting by the fact that a cutaneous reaction similar to that seen in patients with sarcoidosis was also obtained in tuberculin-negative controls.

Attention should be called once more to the suspension prepared from tuberculous lymphomas which acted as Kveim antigen, as well as to the numerous positive Kveim reactions obtained by Sones and Israel with co-workers in patients suffering from tuberculosis. It should be added that, of the few positive Kveim reactions appearing later in Putkonen's control patients, one occurred in a case of lupus vulgaris and another in a case of erythema induratum Bazin. The latent period of the reaction, however, was exceptionally long in these two patients, over one year

in the former case[19 20], and as long as five years in the latter[21]. Might the difference between sarcoidosis and tuberculosis be only a quantitative one? Limitation of time precludes further comment, but even so it is clear that tuberculosis will have to be kept in mind when dealing with the Kveim reaction.

Antigens derived from other infectious diseases causing tuberculoid changes have also been tried on patients with sarcoidosis. In addition, experiments have been made with chemical substances and corpuscular particles which can cause a foreign body reaction of similar structure. However, the cutaneous reactions in patients with sarcoidosis have not differed from those in control persons. The valuable work of the Norwegian Refwem[22] deserves special mention; it is to be regretted that he was not able to review his results personally today.

Despite the wide interest taken in the Kveim test, the active component has not been ascertained. As early as 1943 it was known that the active component is thermoresistant and sinks with the sediment on centrifugation[4]. We also know that it does not pass through a Berkefeld filter and is insoluble in ether[23] — but here our knowledge ends. At the outset it was suggested that the reaction is of allergic nature though its latent period is long. Because of this long latency, some investigators believe that the Kveim reaction is only a sarcoid type of reaction to some non-specific substances. Most present-day authors, however, consider this reaction to be of allergic nature.

In conclusion it should be stressed that the Kveim test is a valuable aid to diagnosis in many unclear cases of sarcoidosis. It also informs us as to the activity of the disease and may play an important part in clarifying its pathogenesis. In the future strong antigens should be aimed at. By using them in suitable dilutions the most selective reactions are obtained for practical purposes, and by studying these strong antigens we come nearer to the truth about the Kveim reaction.

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DISCUSSION

L.-E. Warfvinge, Sweden:

As Putkonen considered the Kveim reaction to be allergic — as did also Kveim is his original report — it should be of interest to know if Putkonen has studied the reaction under corticosteroid therapy. If allergic it ought to be blocked, but as similar reactions can be provoked by many different substances (living or dead tubercle bacilli, leucaemic

gland, normal spleen tissue, quartz and talcum) it seems more likely to be the question of a foreign body reaction which should be less influenced by corticosteroids.

Putkonen:

I have had no opportunity to study systematically the effect of corticosteroid therapy on the Kveim reaction. In sarcoidosis patients under cortisone treatment, however, I have several times observed the disappearance of the reaction papule simultaneously with the disappearance of the skin manifestations, and also the reappearance of both the reaction papule and the skin lesion after interruption of the therapy.

Rolf Lemming, Sweden:

In a paper which appeared in *Nordisk Medicin* in 1937 I gave an account of some attempts to study in greater detail the nature of the tuberculin-negativity, which is so striking a feature of most sarcoidosis cases. Jadassohn had considered this tuberculin anergy to reveal a particular form of high immunity to the tubercle bacillus and had named it specific, positive anergy. In my paper I pointed out that the probability of Jadassohn's theory could be put to a fairly ideal test by infecting the patients with tuberculosis, and I proposed BCG vaccination as a simple and harmless procedure for this purpose. If the tuberculin-negative sarcoidosis patients had never had — or did not have — a tuberculous infection, they should reasonably be expected then to become tuberculin-positive in the ordinary manner and incidence rate. It would then be quite impossible to maintain the conception of positive anergy. If, on the other hand, they remained tuberculin-negative despite BCG vaccination, an unusual mode of immunobiologic response to Koch's bacillus did apparently exist, possibly a positive anergy in accord with Jadassohn's interpretation of this term.

Now it was found that the first sarcoidosis patients BCG vaccinated by me remained tuberculin-negative, curiously enough, even after revaccinations with larger doses of BCG vaccine than those normally used. These results were subsequently (1941—1957) confirmed by eight other authors (a survey was presented). Including my own 19 cases the total of BCG vaccinated, tuberculin-negative sarcoidosis patients amounts to 70. Among these there were but 21 in whom it was possible to achieve tuberculin-positivity (Mantoux, 1 mg.). This implies that there were only 30 % tuberculin-positive, a rate, which is obviously quite incongruous with that of 97—98 % tuberculin-positives obtained on BCG vaccination of healthy tuberculin-negative subjects.

Also in another respect my BCG experiments with tuberculin-negative sarcoidosis patients yielded rather interesting results. In one of my first cases there developed, at the site of BCG inoculation a peculiar local cutaneous lesion, which to my knowledge had never before been observed after ordinary BCG vaccination. An eminent dermatologist, having grossly examined this tumour-like lesion, diagnosed it as a cutaneous sarcoid fully typical in every respect, and on histopathologic examination the picture proved identical with that seen in instances of sarcoidosis. At the 12th Northern Congress of Phtisiology in Stockholm, 1941, I had the opportunity of showing colour photographs of this lesion, which might be regarded as the first sarcoid experimentally produced. Already at an earlier date — *inter alia* in a paper read in Svenska Läkarsällskapet in 1940 — I had emphasized that BCG vaccination in cases of Schaumann's disease may be useful in diagnosis, partly in regard to the behaviour of the tuberculin test after vaccination, and partly through the information obtained by biopsy of the BCG papule 6-8 weeks after vaccination. This special procedure of examination was subsequently, with various modifications, adopted also by other workers (here a survey was presented of such experiments).

The inference to be drawn from the experiments referred to must be that tubercle bacilli, whether BCG bacilli of low virulence, bacilli of normal virulence, or killed bacilli, on inoculation into the skin of a tuberculin-negative patient suffering from Schaumann's disease are capable of giving rise to the typical histologic picture of sarcoid. This fact in addition to earlier evidence, *viz.,* that no tuberculin response develops in these patients after BCG vaccination, can indubitably be adduced at least as support for a hypothetical positive anergy. This, however, would according to Jadassohn imply a mode of reaction including both a very pronounced allergy and a high immunity to tubercle bacilli. *Inter alia,* this might explain why tuberculin intradermally administered is so rapidly disintegrated that there is no time for a grossly visible response to develop, and also why tubercle bacilli can be so rapidly destroyed, *e.g.,* on haematogenic dissemination. In this manner an explanation might be obtained of the fact that tubercle bacilli are so rarely found in the tissues.

Of late I have examined my cases from this point of view, and this has been rendered possible by applying staining methods for tubercle bacilli to the histological sections of BCG papules as carried out by the pathologist, Fredrik Wahlgren. Dr. Wahlgren himself has in his reports stated the amounts of bacilli present in the sections. (In the form of a table a survey was here presented of both the histology of the separate papules and the amounts of bacilli found in the sections.) Among 19 papules removed for biopsy 5 have not been examined as to bacillary

content. This group includes 1 of the 4 histologically typical sarcoids developing after BCG. As regards the remaining 14 papules, I was surprised by the fact that with regard to the amounts of bacilli in the sections they were of two entirely different types. In one group (8 specimens) everywhere in the sections tubercle bacilli were "abundant" or "ample" (Dr. Wahlgren). The histological pictures ranged from tuberculoid structures to classical tuberculosis with necrosis — but there were no pictures typical of sarcoidosis. The demonstration of large amounts of BCG bacilli (of low virulence!) in sections referred to this group appears incompatible with the supposition of a positive anergy, and provides actually a powerful argument *against* a tuberculous aetiology.

When we consider the other group (6 specimens), we find that this is quite different in character with very few, if any, bacilli in the sections. The histological pictures are also here variable, but there is no classical tuberculosis, and it is noted with interest that the remaining experimental sarcoids (3 specimens) appertain to this group. Subjects referable to such a group, *i.e.*, those (i) responding to BCG with granulomas in which bacilli are exceedingly sparse and which in certain instances are identically similar to lesions of Boeck's sarcoid; and (ii) remaining tuberculin-negative after BCG vaccination, undeniably present a mode of reaction very strongly suggesting a positive anergy and hence also the possibility of a tuberculous aetiology.

It is probable that the cases of sarcoidosis where the aetiology may be tuberculous constitute a small group, but I am fairly convinced of their existence. In the overwhelming majority of instances of sarcoidosis, however, the aetiogenesis is still obscure. On the other hand, also these cases are characterised by a peculiar mode of immuno-biologic reaction to tubercle bacilli, which would seem to emerge from the BCG experiments and investigations here summarily reported.

Largely a brief abstract of a paper read at the meeting of Svenska Lungläkarföreningen in Stockholm, November 1957, and to be published separately in *Acta Tuberculosea Scandinavica.*

EPIDEMIOLOGY AND INCIDENCE OF SARCOIDOSIS

By

H. J. Ustvedt

A survey dealing with the racial and age predisposition of sarcoidosis, relationship of sarcoidosis to various geographic and physiographic areas, and the frequency incidence of sarcoidosis in the Scandinavian countries.

FROM THE CENTRAL HOSPITAL OF FREDERIKSBORG AMT,
HILLERØD, DENMARK,
CHIEF: POUL BONDO GRAVESEN, M.D.

CLINICAL FEATURES OF SARCOIDOSIS, ITS INITIAL STAGE, ACTIVE PHASES, HEALING OR HYALINISATION, PROGNOSIS, AND DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS IN THE PULMONARY LESION

By

P. B. GRAVESEN

A detailed description of the clinical features of sarcoidosis requires a thorough knowledge of several specialities; in the daily routine we consult our colleagues who are specialists in other fields of medicine when our patients are to be examined and treated, and here we require especially the assistance of dermatologists, ophthalmologists, otologists and neurologists.

THE VARIOUS MANIFESTATIONS OF THE DISEASE

The radiological examinations of the thorax which have gradually become very extensively used have shown that the skin affection is not the most frequent form of sarcoidosis and have resulted in the demonstration of a greater number of cases than before. It has appeared at autopsies that the localisation to the lungs is surpassed in frequency only by the affection of the lymph glands.

This is in quite good accord with the division into stages of intrathoracic sarcoidosis, where the dissemination in the lung fields follows a period with bilateral glandular enlargement in the hilar areas.

It is even probable that a dissemination into the lung fields is always preceded by enlargement of the hilar glands; and when this is not found it is only due to the fact that radiography has not been performed at this time.

The initial stage may follow a course without symptoms other than the glandular enlargement, possibly with slight dissemination, which can be revealed in the radiogram, a typical lymph node biopsy, and the finding

of a negative tuberculin reaction. In Scandinavia, however, the initial stage will be revealed in a number of cases, most frequently in women, by erythema nodosum which resembles the erythema nodosum in other diseases with an increased sedimentation rate, a rise of temperature, and joint symptoms.

The affection of the joints may persist for a long time during the course of sarcoidosis, no doubt especially in the presence of large intrathoracic processes (as has also been seen in other diseases of the lungs, such as, for instance, tumours).

During the early course of the disease we also find the eye affected, most frequently simultaneously with enlargement of the hilar glands and dissemination or with the glandular enlargement alone, — here the intrathoracic processes will often subside rather soon, so the disease has a more subacute course.

In most cases a nodose or serous iritis is found, but also other parts of the eye may be involved, then often along with the later manifestations of the disease.

The affection of the eye, too, may have its accompanying symptoms; these may be granulomas of the salivary glands, the lachrymal glands, the pituitary gland, or the cranial nerves, possibly several of the localisations at the same time (for instance, during the course of the disease termed subchronic uveoparotid fever, Heerfordt). These manifestations may also occur in other combinations, possibly without any affection of the eye.

Healing may take place in both the initial stage and the fairly subchronic forms, but otherwise the disease passes through prolonged stages with varyingly active phases on to a hyalinisation. According to the parts in which the disease has become localized, the hyalinisation plays a greatly variable rôle and is possibly of greatest significance in the lungs.

The most chronic forms are found among the cases seen by the dermatologists; here the disease may progress or improve, at times heal in one part whilst it progresses in another; old Kveim reactions may be seen to recur and to subside without any particular rhythm, not even necessarily in time with fresh manifestations on the skin. The affection of the bones, too, is found at rather advanced stages with a markedly chronic course.

A feature of interest is the localisation to old cicatrices, which may be seen at a very early stage. As in other organs, the nodose form may be predominant (with distinctly positive diascopy), or the erythema may prevail (as in lupus pernio with negative diascopy). The same difference in nodose and more diffuse types is seen in all manifestations.

In contrast with tuberculosis, sarcoidosis is often localized to the muscular connective tissue, including that of the myocardium.

Splenomegaly may be present, possibly with thrombocytopenia, though this is far from being a constant phenomenon; on the whole, it applies both to the spleen, liver and kidneys that the function of these internal organs is very slightly influenced, though they are frequently involved, for in autopsy findings the order of frequency is first the glandular system and the lungs, followed by the spleen, the liver and the kidneys, and only after the myocardium comes the skin as the seventh in frequency.

Among endocrine organs, symptoms from the pituitary gland are most frequently found, often along with symptoms from the central nervous system and in the form of diabetes insipidus, which is encountered in about 25 per cent of the sarcoidoses of the central nervous system.

Enlargement of the lymph glands may also be found during the late course; the dermatologists have drawn attention in particular to the enlargement of the cubital glands, which are all large, firm, even hard at times, with a smooth surface, and amazingly freely movable in relation to the skin and the underlying tissues.

PROGNOSIS

The association with the lymphatic system motivated Schaumann's term, benign lymphogranulomatosis; today there is possibly a greater tendency to connect the disease with the collagenoses. However, the term benign may possibly have implied too much generalisation, as vision may be lost completely, the dyspnoea may become disabling, possibly give rise to cor pulmonale, the localisation to vital centres in the central nervous system may lead to death, and sudden deaths of rupture of the spleen or of heart-block have also been seen.

These deaths were not very well known at the time when Schaumann chose the name of the disease; at that time one of the most frequent causes of death was pulmonary tuberculosis, which still threatens these patients, who, to all appearances, are more readily infected with tuberculosis than healthy individuals.

However, if we include the great number of cases of enlargement of the hilar glands which never progress and even subside in a very short time, we must admit that, broadly speaking, the disease must be considered benign.

Therefore, I prefer to describe the prognosis in a different way: It depends on the spread of the disease in the organism, it is generally benign in the glandular system, it is not always good when the disease affects the eyes, it depends on the duration in the lungs, is remittent for prolonged periods in skin and bones, is greatly dependent on the localisation in the

central nervous system, but most frequently fairly good, and in the internal organs the course of the disease is so cloaked that only the most massive forms, or the most active periods, are diagnosed; but in the heart the prognosis is bad because the auriculoventricular band is so often involved.

It is difficult to distinguish recurrences from periods of recrudescence, as the criteria of complete healing are too uncertain.

Hyalinisation in the lungs, rigidity of the tissue, and the impaired blood flow are causes of cor pulmonale; it is also possible here that bronchostenoses and the formation of very large cysts may make the prognosis worse.

THE LUNGS

It is difficult to establish the activity diagnosis, partly because radiograms of the lungs must be taken so often that fresh infiltrates may not already have passed an active stage when the radiogram is taken, partly because differences in the exposure may mislead the estimate. Furthermore, the certainty of the diagnosis is of great importance in this connection, for if laboratory investigations are to tell us something about active phases we must be sure that the case from which the laboratory test values are estimated is actually case of sarcoidosis; much work must thus be done to exclude the possibility of other diseases. Here the following diseases should be considered in particular: Tuberculosis, silicosis, pulmonary congestion, widespread bronchiectases, Hodgkin's malignant lymphogranulomatosis, toxoplasmosis and ornithosis, and leukaemic pulmonary infiltrates. The other collagen diseases like periarteritis nodosa and Hand-Schüller-Christian's disease may also resemble sarcoidosis in the lungs; and recently we have had the opportunity in Hillerød to see bronchiologenic carcinosis present a course which bore a close resemblance to sarcoidosis.

A number of pictures are shown to demonstrate that radiograms of the lungs in sarcoidosis may resemble those seen in several other diseases of

CONCLUSION

Figures have been avoided in this survey, and it will be seen that there is no definite nosology in this disease, it may often be elusive in its course and almost without symptoms, but may nevertheless be fairly severe in several cases.

DISCUSSION

Ingrid Gilg, Denmark:

In relation to the very numerous cases of sarcoid described in the literature, very little has been published concerning their localisation in muscles. A very valuable contribution to the study of this problem has been given by the late neuropathologist, Dr. G. Vraa Jensen, with whom I collaborated in the team work of which Dr. Gravesen will speak later.

Within a period of two years Vraa Jensen demonstrated sarcoids in the muscles of 12 patients. At this time there had been published in the entire world literature a total of only 32 cases with this localisation — therefore this was an astonishingly large number of cases.

The explanation for this is that while most of the previous investigators have only looked for granulomas in a single specimen, Vraa Jensen per patient. It was found that one could be fortunate if the first examined examined entire blocks in 10 very large sections — i.e., 300 to 400 specimens per patient. It was found that one could be fortunate if the first examined specimen exhibited granulomas.

It is therefore necessary, if the report is: No muscular sarcoid, that we are informed how many specimens were examined.

Using this technique it appeared that in our series all the patients with diagnosed sarcoidosis also had sarcoids in the musculature.

However, also in this connection there is — as is always where sarcoid examination is concerned — the problem of control material.

Is it not possible in all muscle biopsies to find tuberculoid granulomas, regardless of the disease the patient may have? Here especially lies the problem in the case of patients suffering from tuberculosis.

By that time Vraa Jensen had examined during ten years numerous muscle biopsy specimens from patients with medical and neurological affections (at least 5 specimens were examined in each individual case) and in only a single case had he found a granuloma in a patient who did not have sarcoidosis.

At the same time the examination was begun of muscle biopsy specimens from tuberculous patients hospitalised at the Øresunds-hospitalet in Copenhagen. Vraa Jensen was engaged in this work when he died. At least 25 patients had been examined and no granulomas could be demonstrated in the musculature of any of these patients.

Muscular biopsy will probably never be significant as a diagnostic means, but for research purposes I consider this examination extremely valuable. Especially I feel that attention should be directed towards the combination of severe muscular and heart sarcoidosis. We have seen two or three cases at autopsy.

DIAGNOSIS OF SARCOIDOSIS

By

Bo Carstensen

During the past ten years slightly over 300 cases of sarcoidosis have been diagnosed at Sollidens Sanatorium. Three fundamental conditions were set up for the diagnosis of this disease, as follows:

I. *Typical clinical and/or x-ray picture*
A typical case history, "multilocalisation", discrepancy between outspread organic changes and relative absence of symptoms, hyperglobulinaemia, etc.

II. *"Exclusion methods"*
E.g., by thorough examinations other imaginable diseases must be excluded: tuberculosis, pneumoconiosis, systemic diseases (e.g., Hodgkin's etc.), neoplasm, mycosis, etc.

III. *Biopsy* — with histological support for the diagnosis of:
a) Spontaneously changed tissue (usually *retroclavian bloc dissection a.m. Daniels)*
b) Provocative changed tissue (Kveim's, Lemming's, Warfvinge's skin test).

In the author's opinion the diagnosis may also be made on the basis of only the first two conditions, but multilocalisation into not less than three organs is then required. X-rays of the skeleton of the hands and feet with one or more typical cysts may frequently be a good aid to diagnosis.

The best method of biopsy in cases of suspected intrathoracic sarcoidosis was found to be lymph node biopsy by the method of Daniels. From January 1952 to May 1958 a total of 421 biopsies of this kind were performed (Odelberg, later Rentzhog). Table 1 shows the results of the biopsy examinations. (Editor's abstract.)

TABLE 1.

Biopsy a.m. Daniels in 421 obscure lung cases. Definitive clinic diagnosis.

Preliminary		After Biopsy, Confirmed as or Altered to				Still Uncertain	Biopsy of No Aid to Diagnosis because	
		Sarcoidosis	Tuberculosis	Hodgkin's Disease	Carcinoma	Tuberculosis? Sarcoidosis?	No Nodes Found	Node Nonspecific or Normal
Sarcoidosis or Sarcoidosis?	330	197	3	1		2	6	121
Tuberculosis? Sarcoidosis?	33	5	7			1		20
Neoplasm? Tuberculosis?	46		3		6	1	1	35
Open	12							12
Total	421	202	13	1	6	4	7	188

FROM THE DEPARTMENT OF PULMONARY DISEASES, ST. GÖRAN'S HOSPITAL, STOCKHOLM, SWEDEN, CHIEF: SVEN LÖFGREN, M.D.

METABOLIC ASPECTS OF SARCOIDOSIS

By

SVEN LÖFGREN and RENÉE NORBERG

Regarding the metabolic aspects of sarcoidosis I shall restrict myself mainly to reporting on our experience as to renal function and hypercalcaemia.

As is well known, Salvesen in 1935 drew attention to a peculiar kind of renal involvement in a sarcoidosis patient: there was in his case a slight proteinuria, a considerable decrease in function with urea retention and hyposthenuria, but no haematuria, hypertension or cardiac hypertrophy. Subsequently similar observations were described by other workers.

In 1939 Harrell & Fisher gave an account of hypercalcaemia in some sarcoidosis patients without impairment of renal function. Subsequently hypercalcaemia associated with sarcoidosis has been reported by several workers. In many instances, hypercalcaemia occurred coinjointly with impaired renal function, but in several of the cases on record no signs of renal disease were to be demonstrated.

Our knowledge of the patho-anatomical basis of the functional changes just mentioned is by no means complete. For this reason we have carried out comparative studies of the function and histopathology of the kidneys in a number of cases of generalised sarcoidosis. For the histological examination aspiration biopsies were carried out.[1]

So far the series includes sixteen cases, six with and ten without hypercalcaemia.

All the six cases with hypercalcaemia presented moderate to serious impairment of renal function, and in the renal biopsy specimens pronounced lesions of the type previously described in occasional autopsy cases.

Hence, a more or less marked thickening and hyalinisation of Bowman's capsule was invariably demonstrated in a portion of the glomeruli; occasionally, a glomerulus was replaced by connective tissue. In five cases

[1] S. Löfgren, B. Snellman and Å. G. H. Lindgren: Renal Complications in Sarcoidosis. Acta med. Scandinav. 1957:159:295.

scattered deposits of mineral salts (presumedly calcium phoshate) were noted, partly in the interstitial connective tissue and partly in the tubular lumen; in three instances interstitial epithelioid cell granulomas with structures typical of sarcoidosis were observed.

The clinical picture associated with this renal damage — apart from functional impairment — was rather deficient in symptoms: no hypertension, slight albuminuria, if any, and spun deposit normal or mildly pathological. The hypercalcaemia did not exhibit any relationship to the amounts of proteins or inorganic phosphate in the serum. Of the clearance tests, PAH clearance as a rule was more markedly depressed than creatinine and inulin clearances, respectively. This difference would seem to suggest damage to the tubules.

The findings were quite different in the ten cases of generalised sarcoidosis without hypercalcaemia. As to the renal function, this was but occasionally mildly impaired. The histological lesions noted in biopsy specimens within this group were, as a rule, so inconspicuous and indefinite that they could not confidently be interpreted as having been caused by sarcoidosis.

Hence the essential information supplied by this sarcoidosis material is that definitely abnormal renal changes were demonstrable by studies of function and histo-pathology only in those instances where hypercalcaemia was present. This would seem to suggest that the renal damage in cases of sarcoidosis were secondary to the hypercalcaemia.

As is well known, the origination of hypercalcaemia in sarcoidosis has not been satisfactorily explained. In the main, three suggestions have been advanced: that it is due to the disturbance of plasma proteins, that it is a manifestation of parathyroid hyperfunction, or that it results from bone destruction by sarcoid invasion.

The first theory could not be maintained for two reasons: the calcium level in the serum does not vary in proportion to either the total serum protein, albumin, or globulin contents, and further, under normal conditions albumin and not globulin is the protein chiefly concerned in calcium linkage; in sarcoidosis, as is well known, it is the globulin fraction that is increased.

Parathyroid hyperplasia has been reported in some cases of sarcoidosis with hypercalcaemia, but in other instances surgical exploration has shown the glands to be normal. In none of the cases on record was there a decrease in the amount of inorganic phosphate, which is definitely adverse to the idea of parathyroid hyperactivity.

It has been postulated by some authors that the marked rise in blood calcium might be connected with osseous involvement, particularly since the alkaline phosphatase in the serum may also be moderately increased.

On the other hand, some workers considered bone involvement and hypercalcaemia to be independent and suggested that the disorder of calcium metabolism starts in the blood rather than in the bone.

In our attempts at solving the problem of the cause of the hypercalcaemia we have not been more successful than other workers. However, I should like to describe an observation on the significance of which we have much speculated, viz., the hyperuricaemia frequently found in instances of sarcoidosis. For example, when cases of sarcoidosis are compared with cases of tuberculosis, there is, as will be seen, a significant difference in the uric acid content of the blood (Table 1).

TABLE 1

N.P.N. and uric acid in 47 cases of sarcoidosis and 120 cases of tuberculosis

	N. P. N. mg%	No. of Cases	Uric Acid $\geq$ 3.5 mg% No. of Cases	Uric Acid $\geq$ 5.0 mg% No. of Cases
Sarcoidosis	< 35	30	22 (73.3% ± 8.0)	9 (30.0% ± 8.4)
Tuberculosis		67	21 (31.3% ± 5.7)	3 (4.5% ± 2.5)
			D:42.0% ± 9.9***	D:25.5% ± 8.7**(*)
Sarcoidosis	35—44	17	14 (82.4% ± 9.3)	10 (71.4% ± 11.0)
Tuberculosis		53	38 (71.5% ± 6.2)	3 (5.7% ± 3.2)
			D:10.9% ± 11.2)	D:65.7% ± 11.4***
Sarcoidosis	< 45	47	36 (76.6% ± 6.2)	19 (40.4% ± 7.2)
Tuberculosis		120	59 (49.2% ± 4.6)	6 (5.0% ± 2.0)
			D:27.4% ± 7.7***	D:35.4% ± 7.4***

In this table the cases are divided into two groups, one with an entirely normal non-protein nitrogen rate, below 35 mg%, and another group with a very slightly elevated rate, 35 to 44 mg%. In several of the subgroups and, above all, in the collected series a significant difference is revealed between cases of tuberculosis and of sarcoidosis as regards the uric acid content.

The estimations of the uric acid content reported just now were carried out with Folin's method. This, as is well known, yields too low uric acid values. The method of choice is the enzymatic method in which uricase is used; this procedure yields higher, adequate values. To a limited extent it was possible recently to use this method, and we were able to corroborate the observation that patients with generalised sarcoidosis have a higher uric acid blood level than controls. Whether this hyperuricaemia is due to an increased production of uric acid or to a decreased destruction, or to a decreased elimination, we cannot say at the present moment.

In a preliminary study we have followed the correlation between uric

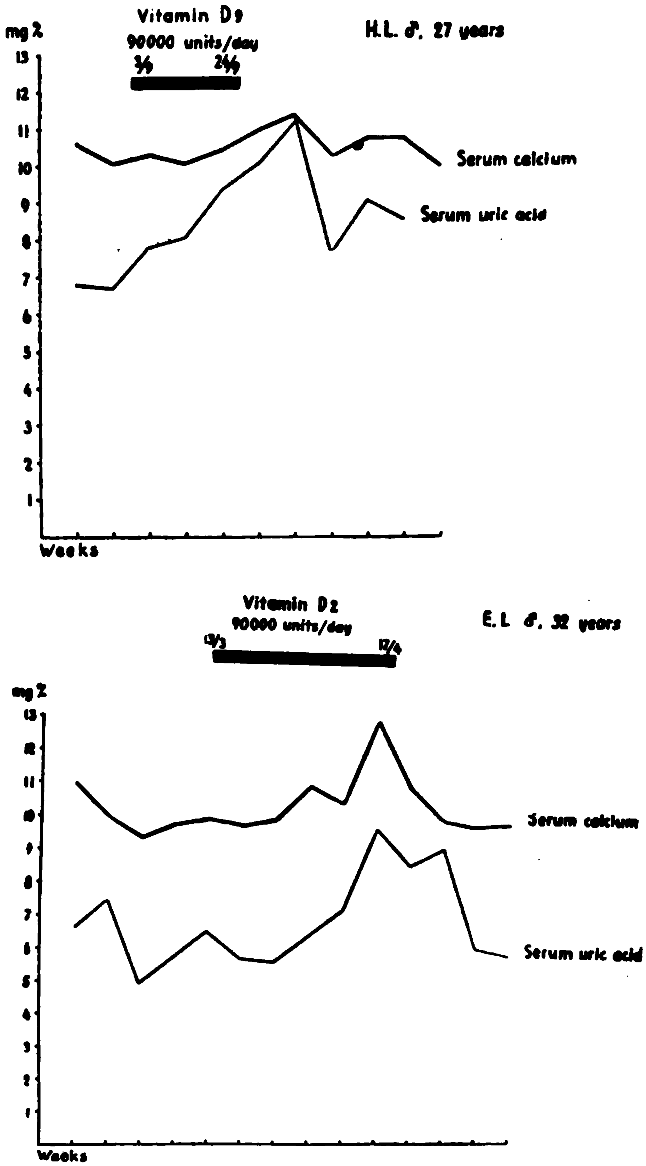

Fig. 1. Simultaneous rise of serum calcium and serum uric acid (enzymatic method) in two cases of sarcoidosis treated with calciferol.

acid and calcium in the blood during calciferol treatment of sarcoidosis. Invariably the uric acid content was found to rise to very markedly pathologic values parallel with the development of hypercalcaemia (Fig. 1). We are not prepared to give an explanation of this observation, but we have asked ourselves whether the hyperuricaemia might possibly be a factor which contributes to the onset of hypercalcaemia in patients with sarcoidosis.

THERAPY OF SARCOIDOSIS

By

Bo Carstensen

A survey is first made of early therapeutic attempts, the author stating that all reports on attempted therapies and results of therapy in cases of sarcoidosis up to 1951 are conflicting and unconvincing.

When reports were received concerning adrenocorticotropin and cortisone and the biological effect of these hormones in arresting inflammatory reactions, and not the least concerning their inhibitory effect on the development of granulomas, it was quite natural that good results were to be expected from these hormones in sarcoidosis. As is well known, this disease is characterised especially by widely spread epithelioid cell granulomatosis. In May 1951 this therapy was taken up for trial at Sollidens Sanatorium and a total of 130 cases have been treated.

In patients with sarcoidosis of the lung the effect was good in recent cases of miliary type. However, the high tendency of this type to spontaneous remissions must be held in mind. In the type with large patches and in the confluent infiltrative type the effect was considerably poorer and possibly doubtful — even in recent cases. In fibrous sarcoidosis of the lung of older standing there was only subjective amelioration, which nevertheless in some cases was considerable and an important and welcome relief for the patient.

In cutaneous sarcoidosis the effect of steroid therapy was less beneficial in the author's experience; this was especially true of lupus pernio. When the disease was localised to the eyes, heart, kidneys or the central nervous system, the author considered an attempt with steroid therapy absolutely indicated, since this might prove life-saving or conserve vital or indispensable organic functions.

No serious untoward effects were seen. There had developed no cases of tuberculosis or suspected tuberculous disease in the author's series of cases. (Editor's abstract.)

REHABILITATION OF LUNG PATIENTS DURING SANATORIUM TREATMENT

By

ERKKI LARMOLA[1]

In taking care of a patient suffering from pulmonary tuberculosis — or from a chronic pulmonary disease in general — it is not sufficient to prescribe sanatorium treatment for a few months, to give antibiotics, and, when necessary to perform an operation. If we restrict our help to the medical treatment only and release the patient as soon as this is finished, we jeopardize everything that has been gained with much work and care. The goal is not reached before the patient is rehabilitated, i.e., before he has returned to the community as a worker, capable of taking care of himself and his dependents.

From the viewpoint of rehabilitation the tuberculous patients are in a particular position because of the infectiousness of their disease. Fear of infection meets them everywhere and is perhaps a greater obstacle to their rehabilitation than their lowered working capacity, which mostly depends on the reduced function of the lungs and circulation more than on the activity of the disease. They *have been* tuberculous and *are* lung invalids.

I am of the opinion that the risk of tuberculous infection is still too much stressed — even in medical literature. As a bacteriologist and a clinician I have been exposed for more than thirty years to infection by tubercle bacilli both *e vitro* and *e vivo,* but I have never had cause to regard this danger as significant, either for myself or for my assistants, and I am sure that this conviction has saved us from needless worry in our work. If we cannot convince the general public — and many of our colleagues as well — of the fact that, even though tuberculosis is a contagious disease, its contagiousness is mostly overrated and that infection can be prevented by relatively simple measures, we shall meet very great difficulties in our efforts to rehabilitate our patients.

In Finland we are now speaking of *medical rehabilitation* as conceptually different from *social rehabilitation.* The former does not imply the medical

[1] Kiljava Sanatorium, Kiljava, Finland.

treatment as such, but something complementary to it. It may be defined as including all those measures that are needed for rehabilitation beyond the actual medical treatment and are performed at doctor's orders and under his direct guidance.

Most doctors who work in the field of rehabilitation will perhaps stress that all through the process the physician must be the central person, the leader of the working team. My opinion is that this is neither necessary nor desirable. A recovering patient will reach a point when sanatorium treatment and medical rehabilitation are completed, and the essential need is to find a new position for him and perhaps to give him necessary training. The doctor is not qualified to solve these problems, because he is neither an educator nor a sociologist. At this point he should retire to the position of a counsellor and let others take over the lead in the social stage of rehabilitation work.

It is regarded as a fundamental principle of rehabilitation that the work must begin as soon as the disease is diagnosed and the patient has arrived at the sanatorium. Of course, this does not mean that the patient must be submitted to active work, training and schooling from the very beginning. The first task is to determine the patient's need for rehabilitation and his qualifications, thus: how does the disease change his position as a working member of the community and what kind of help does he need to adjust himself to this changed position, and, secondly, what kind of faculties and abilities he has or will have to fulfil the requirements of a new job or to receive training needed for a new employment. It is the social worker who should clear up the first problem. The second belongs in the sphere of the psychologist and the educator, but in both cases the verdict of the doctor is decisive. The doctor alone can estimate whether the decrease of the patient's working capacity is temporary and whether he may return to his previous work, or if it will be necessary for him to find a new occupation and if a given type of work will then be suitable or not. The doctor must also judge to what degree the patient's own wishes and plans may be taken into consideration in planning his rehabilitation. However, if the doctor will make the decisions alone, in many cases the result will be advice that cannot be taken, as it is based on the medical viewpoints only and leaves the economical, social and vocational aspects without consideration — because the doctor is not an expert on them.

Thus, team-work will be necessary from the very beginning, and the doctor can lead it only if he has some insight into the special areas covered by the others. It is easier for him to make himself acquainted with these than for the others to acquire the necessary knowledge in medicine.

As for the other team- members, the participation of the social worker

begins at once, because the need of rehabilitation can be determined earlier than the suitability of the patient for work and education. With a view to the planning of the rehabilitation process, both the temporary and the permanent invalidity as well as the intellectual qualifications of the patient must be estimated as soon as possible during his stay in the sanatorium.

The process of rehabilitation is often divided into three stages: "diversional therapy", "occupational therapy", and "vocational therapy". The first-mentioned we have practised for a long time. Personally, I have often wondered if we have not succeeded perhaps too well in our efforts to destroy the stamp of hospital from our sanatoria. In principle I am against the regimen of prolonged "strict bed rest", because I think that as treatment it is necessary only in selected cases and should be avoided as detrimental to rehabilitation. But to take as much time as possible from the sanatorium routine for arranging light diversional entertainments is not rehabilitation. The patient's intellectual activity and capacity should be used more profitably and directed to practical instruction.

It is often emphasized that the purpose of occupational therapy is to keep the patient's mind and hands busy, to lead his thoughts away from brooding on his disease. The nature of the occupational work is regarded as being of secondary importance. This may be sufficient in cases where the patient will be able to return to his earlier work or where he is incurable and needs mental support, but when further rehabilitation is required, also occupational therapy should be planned in such a way that it will be useful for the later stages, including as much vocational therapy as possible.

Shortly after the war there was established in Finland a special institute, the Sanatorium Institute for planning and directing the diversional and occupational therapy in our sanatoria. During the first years its main line was general and social education. The patients entered the courses eagerly, but their interest was of short duration and the practical benefit from the courses was small. Now the programme is completely remodeled. Instead of arranging courses that correspond to the education given in secondary schools, the instruction is concentrated on courses preparing the patients for vocational schools or training them in practical skills.

Of course, complete vocational training cannot be given during the treatment in sanatorium. Among the participants there are many who never will be able to pursue a craft or trade. The patients enter the courses and leave them at unpredictable points according to the progress of recovery. When the convalescent has reached a stage at which he can do active work for more than three hours a day, he will leave the sanatorium. If he can then return to his earlier work — perhaps gradually and helped by ambulatory chemotherapy — he is fortunate.

Many patients, however, are not in this fortunate position. We calculate that about 10 per cent of the patients who are leaving our sanatoria both need further rehabilitation and are capable of profiting by it. Of course, all of them will not require vocational training to enter a new trade and, besides, during medical treatment in a sanatorium it is in most cases too early to determine if a convalescent will stand 2—3 years' intensive work in a trade school. This school is both exacting and expensive and the trainees must therefore be carefully selected. This entrance selection is the main reason for the fact that lung invalids, especially former tuberculous patients with their possibility of relapse, cannot compete with healthy young people for entrance into schools that are free for all, but they must have special schools where they have the right of precedence. Even in these, of course, it must be presupposed that already at the entry the condition of the trainee is stable and relapses are not expected.

The step from sanatorium directly into a vocational school is too radical, more time is needed for selecting the most suitable material for training. In Finland we have, in consideration of this, made plans for attaching a rehabilitation department to most of our large central sanatoria. In this department the convalescing patients would still be under continuous medical control, there being, however, better possibilities than in the sanatorium proper to arrange preparatory vocational schooling. The patients who are most in need of further rehabilitation could be picked out there and directed to the various channels for post-medical rehabilitation. This department would thus work like a rehabilitation centre, but the convalescents would enter earlier, already at the quiescent stage of their disease, and it would not be independent but an integral part of the sanatorium.

On account of economic difficulties we have not been able to fulfil our programme. Only two such departments are in operation. The experience gained from them is promising. They fill the gap between hospital and vocational school, and they are much less expensive than special schools or colonies for tuberculotics. There we can reach the highest stage of what we call medical rehabilitation and pick out such patients as are most suitable for special training, thus saving both time and money.

In planning the rehabilitation work it is not appropriate to offer the most expensive to all or even to the majority. The community cannot afford it. We must be prepared to prove that rehabilitation is profitable, that vocational schooling and placement means saving the public funds, not wasting them. Rehabilitation is not charity, its object is to strengthen the foundation of the community — the working capacity of its members.

FROM THE UNIVERSITY CLINIC OF THE HELSINKI TUBERCULOSIS SANATORIUM, CHIEF: PROFESSOR JORMA PÄTIÄLÄ, M.D.

THE POST-SANATORIUM REHABILITATION OF TUBERCULOTICS IN FINLAND

By

JORMA PÄTIÄLÄ

The rehabilitation of patients with tuberculosis is continued also after their discharge from the sanatorium. This post-sanatorium rehabilitation work is of many kinds and depends on the nature of the disease and the occupation of the patient. The patients who return from the sanatorium to the community are grouped with respect to rehabilitation into three categories, as follows:

I) *Mild cases.* The disease was diagnosed at an early stage when no marked changes had as yet occurred, or it has responded so well to treatment that no significant functional restrictions remain.

II) *Lung invalids proper.* In these cases the disease process also has been arrested, or it has healed or is at least in progress of healing, but the disease or its treatment has left a significant permanent functional restriction. If the changes in the lungs are far advanced, there remains after healing a large amount of scar tissue which contributes to the impairment of the lung function.

With respect to all the patients in this group it is implied that the disease or the above mentioned therapeutic measures have left considerable functional restriction. If, furthermore, the process has become arrested and the patient no longer is a contagious risk, he can be considered a lung disabled also within the definition of the Law on the Welfare of Disabled Persons. The current legislation concerning lung disabled persons is based on the amendment of this law which was made effective on January 1, 1953.

According to section 2 of the law, a disabled person is one whose capacity for work and activity is, because of loss or deficient function of an organ, permanently reduced to such a degree that it constitutes an essential detriment to him in his daily life or in the securement of his livelihood.

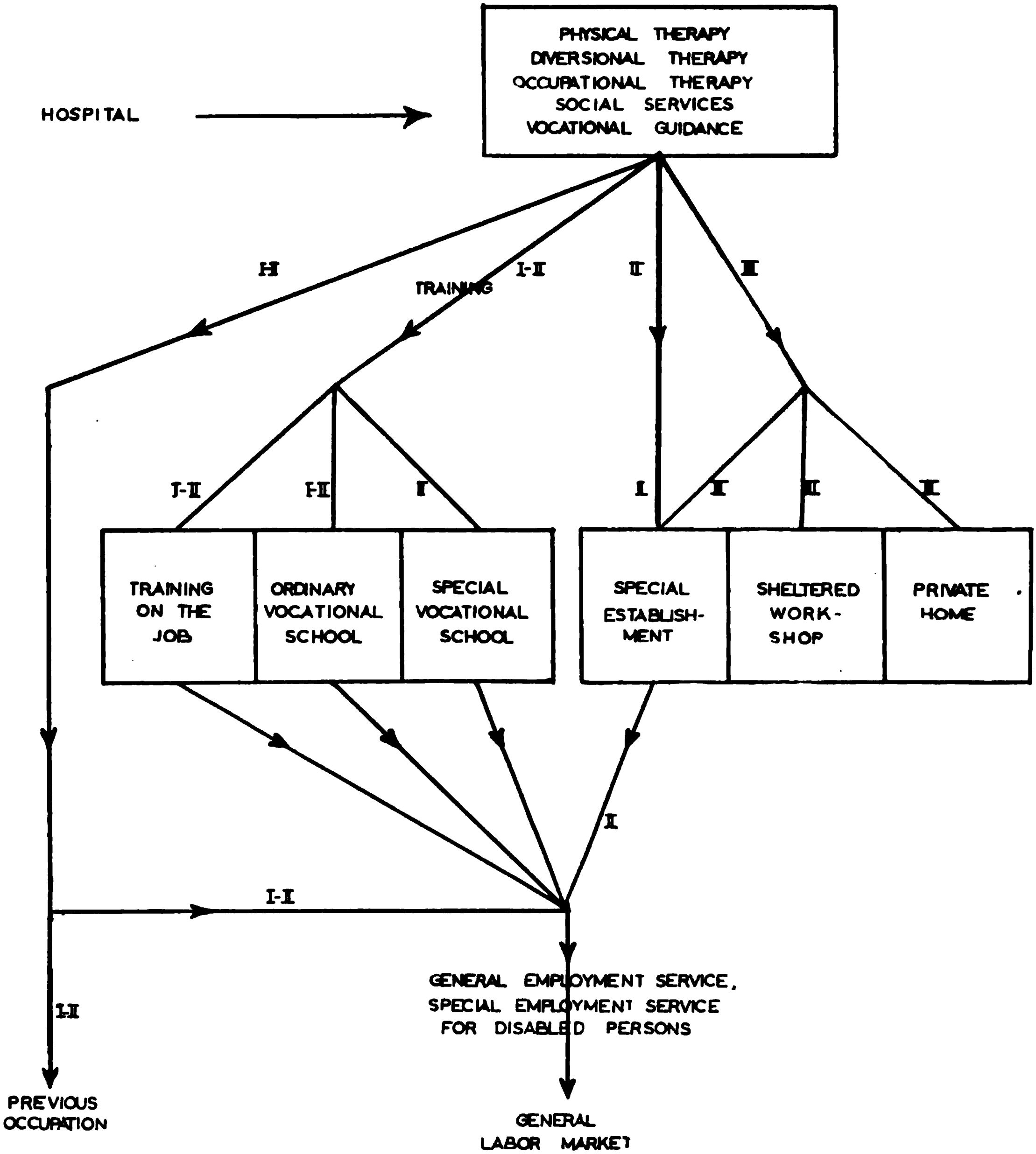
HOSPITAL
PHYSICAL THERAPY
DIVERSIONAL THERAPY
OCCUPATIONAL THERAPY
SOCIAL SERVICES
VOCATIONAL GUIDANCE
TRAINING
TRAINING ON THE JOB
ORDINARY VOCATIONAL SCHOOL
SPECIAL VOCATIONAL SCHOOL
SPECIAL ESTABLISH-MENT
SHELTERED WORK-SHOP
PRIVATE HOME
GENERAL EMPLOYMENT SERVICE,
SPECIAL EMPLOYMENT SERVICE
FOR DISABLED PERSONS
PREVIOUS OCCUPATION
GENERAL LABOR MARKET

Fig. 1.

In the case of a person disabled by tuberculosis, it is a further condition that the disease is not at a contagious stage.

The presence of a tuberculous disease does not in itself provide adequate grounds for the patient to be brought within the scope of the law on the welfare of the disabled, but it also is conditional that the disease has left a permanent and considerable injury.

The percentage of disablement frequently is high during the first few months after the termination of treatment but, as appears from the above, the law implies a final, permanent disability. By a considerable injury is inferred in practice a functional limitation of 25—30 per cent.

III) *Chronics or unhealed patients.* In the third group of patients the disease has not been completely arrested by treatment. It may, however, occasionally be in a quiescent state. Tubercle bacilli are not necessarily always present. The patient's general state of health may be so good that he is occasionally able to work. Because of the variable course of the disease, however, these patients usually are unable to work regularly. In the British and American literature these patients are termed "good chronics", since they are capable of doing light work from time to time.

The patient's way from the sanatorium is determined by the group to which he belongs. The various courses open are seen in Fig. 1.

The first group consists of mild cases. These persons may be regarded as having an almost normal working capacity. Their disease is well healed and the process has not essentially impaired the lung function. They cannot, therefore, be regarded as disabled persons in the sense of the law. The greater proportion of these patients are able, after convalescence, to resume their previous employment or to obtain similar work on the labour marked. It is advisable, however, that persons in this group avoid heavy labour and unfavourable working conditions. In such cases, suitable work should be offered to them by the special employment service for disabled (Fig. 2).

These special employment services are maintained by the organisations of disabled persons and are under the control of the Ministry for Social Affairs, which also defrays all the expenditures of the organisations. The offices serve all disabled persons and not only those disabled by tuberculosis. Especially the younger patients in this group can be given training in a new, more suitable occupation either at their place of work or in public trade schools in the normal manner without receiving exceptional benefits. They are not eligible for training in the special trade schools for the disabled, since their lungs are not injured to the extent defined in the law on welfare of the disabled.

The second group comprises the lung disabled proper. Their rehabilitation after sanatorium therapy depends, above all, on the patient's former occupation, age and nature of disablement.

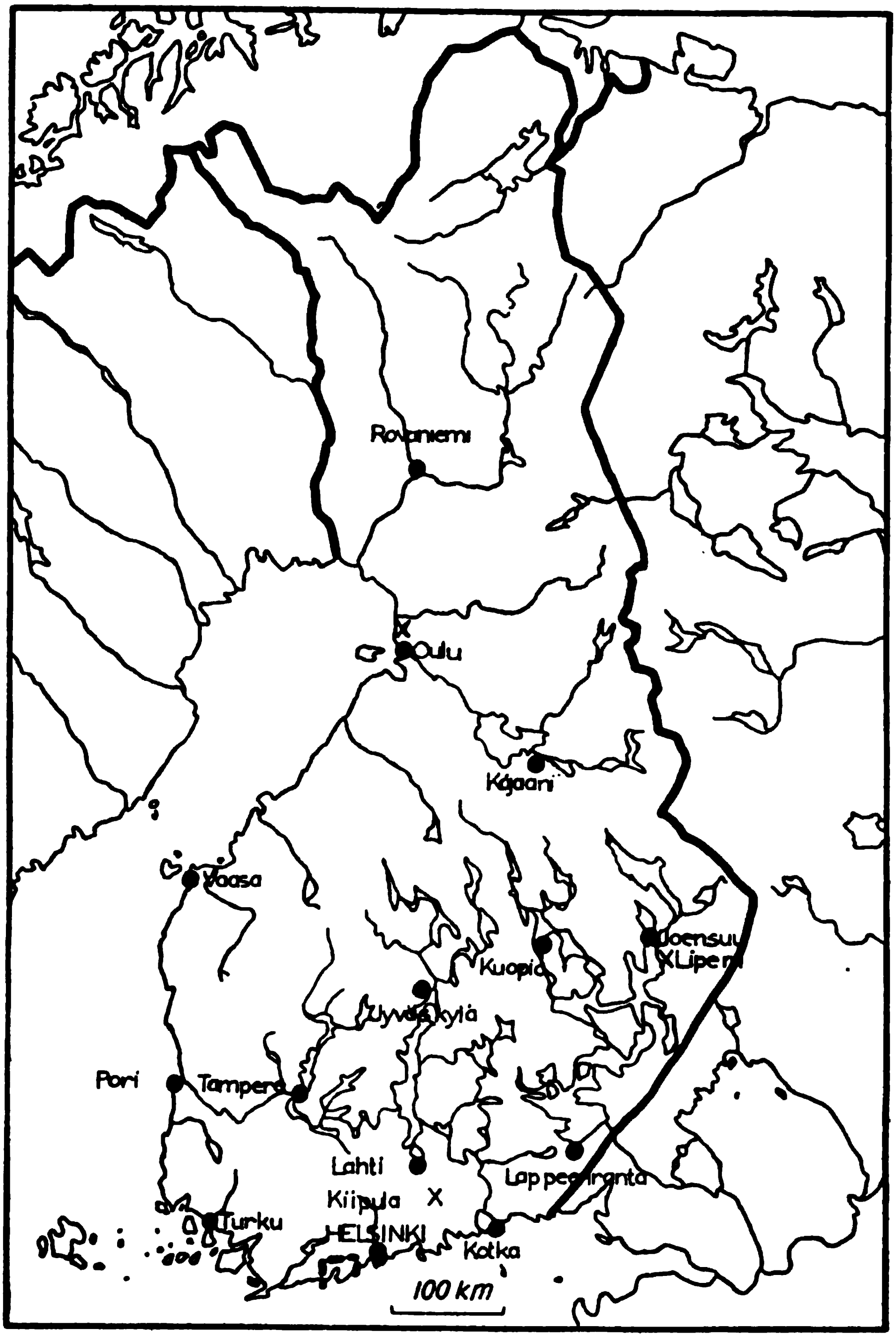

Fig. 2.

● The special employment service point of invalids in Finland.
X The special vocational school.

Many of those who previously have been employed in a light occupation resume this or similar work if they are adequately skilled. On the other hand, it may be very difficult for those who have no occupational skill or who previously have been employed in heavier labour to secure work that is compatible with the degree of their invalidism. In such cases it is important to learn a new trade. As in the first group of patients, the training can be obtained in the usual manner at the place of employment or in public vocational schools, but it also can be obtained in the special trade schools for the disabled under the law on welfare of the disabled. In some countries promising results have been reached in the training of the disabled at the working places, but in Finland this form of instruction has so far been insignificant. The same is true of instruction in public trade schools. The best results have been obtained in Finland by teaching the disabled in their own special vocational schools.

Especially during World War II the vocational instruction of lung invalids became a subject of great importance in Finland, since one-half of the about 14,000 men who acquired tuberculosis in the armed forces were young men aged 17—25 years and most of them had no particular civilian occupation. The so-called vocational instruction of war disabled began already in 1942 with temporary courses, and in 1947 a special vocational school for 150 pupils, open exclusively to tuberculosis and lung invalids, was completed at *Liperi* in Eastern Finland. During its eleven years of activity since 1947 this school has given instruction to about 550 pupils, all of whom have completed a two years' course. The instruction at the school is divided into the following courses of study: metal working, electricity, and wood working.

In addtition to the trade school in Liperi there are two other vocational schools for tuberculosis and lung invalids. The *Kiipula* Vocational School in South Finland, operating since 1955, gives training in office work and gardening to both men and women, and in addtion there are courses in the radio and telephone branches for men. A total of 120 pupils can be accommodated at a time. The courses last 1—2 years.

The third vocational school for tuberculosis invalids is in *Oulu,* in North Finland. Instruction was started here in 1957 for the training of draftsmen, office workers and repair mechanics. The number of pupils is 108 and the courses last two years.

All of the above mentioned schools are under the supervision of the Ministry of Trade and Industry and observe its program of instruction in the same manner as the other trade schools in Finland. The expenses are defrayed by the Ministry for Social Affairs under the law on disabled welfare. In the case of pupils without means the Ministry pays all their expenses for instruction, room and board. Only the pupils in a better financial position pay a part of their charges for room and board.

The pupils are admitted to the schools on the basis of applications submitted to the Ministry of Social Affairs. The entrance requirements include: age 16—40 years, previous education corresponding to a completed primary school course, and tuberculous or lung invalidism. (Cases in an active stage are not admitted to the schools.) In the consideration of the application great weight is placed on the certificate written by a specialist on the applicant's state of health.

In cases in which the Ministry for Social Affairs is unable to obtain sufficient information concerning the nature of the applicant's disease or the appropriateness of the vocation selected by him, he may be summoned to the Examination Centre for Disabled at the Institute for Occupational Health in Helsinki. The examinations last about one week and consist of three parts: a medical, a psychological and a social examination. The examination department follows approximately the same principles as the similar department in Oslo, Norway.

The third group comprises the so-called chronics. Everywhere in the world the care of these patients constitutes a severe problem. They may at times be in a relatively good condition but they cannot work for their living. The prognosis and nature of the disease of the patients in this group differ so greatly that no generalisation of procedures is possible. One of the solutions is to retain them in the sanatorium. This system, however, has both advantages and disadvantages. A definite advantage is that in such a case these patients, which at times are a contagious risk, cannot spread the disease. Furthermore it may be possible that, contrary to expectations, their disease may be healed during continuation of the hospital therapy. Lengthy hospitalisation, however, has the disadvantage that the patient becomes apathetic, reacts negatively towards everything, and has an unfavourable influence on the other patients. In addition, these chronics occupy hospital beds that would be needed by many patients with a better prognosis. For this reason the chronic patients are frequently discharged from the hospital. They may then either return home or be placed in special establishments or in sheltered workshops.

The possibility of *returning home* depends mainly on the economic and social status of the family. If these are good and the patient is middle-aged or elderly, it may be the best solution. Therapy must naturally be continued but the patient can occupy himself with some light work, possibly a hobby.

Another alternative is to enter these patients *in special establishments.* In these, much less staff is needed and the patients have greater personal freedom. Work therapy can be used successfully and may also give the patient some financial remuneration. The best known establishments of this kind are *Papworth* and *Preston Hall* in England, and *Reykjalundur*

in Iceland. The importance of Reykjalundur has been very great for the aftertreatment of tuberculotics in Iceland, since it can, for example, now accommodate all tuberculous convalescents. A part of the patients are given work training and a part vocational instruction. There are no institutions of this kind in Finland, only a small nursing home for so-called war tuberculotics being in operation.

A third solution is that patients in this group are transferred to so-called sheltered workshops where they can perform light work and receive regular medical treatment. Finland lacks also these sheltered workshops. In England this system is highly developed and is called "Employs Factories".

An important special institution from the point of aftertreatment is that at *Appisberg*, Switzerland. It is a work sanatorium, where the patients are accustomed to normal work by gradually increasing their work stress under a physician's supervision. Instruction is also given, for example in commercial fields and metal working.

I have described above the general outline of the rehabilitation work carried out in Finland after the sanatorium treatment of the patients. The greatest advance has been possible, without doubt, in vocational training. The three trade schools for persons disabled by tuberculosis now operating in Finland, which accommodate about 400 pupils, and the other schools for disabled which in special cases also accept tuberculosis invalids are a guarantee that a considerable proportion of suitable applicants can be admitted to them. The problem is greatest with respect to chronics, for it has not been possible to find any general solution which could be widely applied to the chronics.

In concluding there is reason to point out that the rehabilitation work for tuberculotics possesses somewhat different forms in the various countries, for this activity is influenced to a certain extent by the prevailing conditions, for example the country's type of economy, its economic status, and to some degree the characteristics of the people.

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FROM NAKKEBØLLE SANATORIUM,
CHIEF: TAGE HELMS, M.D.

REHABILITATION OF THE TUBERCULOUS IN DENMARK

By

TAGE HELMS

Heaf has defined rehabilitation as the process by which a patient returns to the state of normal life and work that the clinical condition allows. He stresses that it does not merely bring the patient back to work but also to his family and normal environment.

According to Heaf, two factors make rehabilitation particularly difficult for a tuberculous patient, viz., the fear of infection and the fear of relapse. Through many years the tuberculous patient's occupation has been a problem; during treatment in the sanatorium and hospital, where the long idleness has involved a psychic strain, and after discharge, when the natural fatigue of convalescence has made it difficult for him to get going. Lastly, there has previously been an exaggerated fear of infection in a number of workplaces, so that the patients have felt — justly or not — that their colleagues were looking askance at them. When, moreover, many patients were quite naturally afraid that resuming work, particularly strenuous work, would involve a relapse — and they were apt to blame the work for the relapse — it is not surprising that the rehabilitation problem has encountered many difficulties. On the other hand, it has been demonstrated time and again that the very fact of being occupied, of trying to educate themselves, frequently relieves the patients of depressions, and rehabilitation helps improve their economic status.

A comprehensive literature on rehabilitation has accumulated. As early as the beginning of this century a number of sanatoria used occupational therapy, but in too schematic a way. It was only in the form of gardening, cleaning, and the like, and it did not give the patients the feeling which appears to be the essential basis for any rehabilitation: *The feeling that they are being educated at the same time as they are working.* And in the early days the occupational therapy often gave the patients the impression that they were working for the benefit of the institution, not of themselves.

During the first world war Varrier Jones in England started an undertaking on an industrial basis, i.e., by means of modern machinery. This grew into the excellent institution "Papworth", which replaced the earlier training centres with agricultural work, since agricultural work proved to be too poorly paid in England to give the patients satisfactory remuneration.

Rapidly, the problem regarding the patinets' families was raised. Houses were built, and the families moved to "Papworth", a number of the healty members also taking part in the work. From medical quarters it was objected that this made the patients stay on for ever, according to the principle: once tuberculosis, always tuberculosis. For this reason "Preston Hall" was started, where the stay is temporary.

Here the patients received education and vocational training in order to return to normal life. They could only stay while they were being educated. However, some sheltered workplaces were started at the same time, where they could work to begin with. This proved a very expensive scheme, as also emphasised by Heaf, but analysing the present point of view in respect to rehabilitation he concluded *"that rehabilitation is an extremely important and very necessary link in combating tuberculosis, that it is an inevitable link in the treatment, and that the gradual rehabilitation reduces the incidence of relapse.*

In Denmark, where good economic support is granted to help the patients, the rehabilitation programme must be the joint concern of physician, social worker, and patient. From the first day of illness the patient must be made to realize that by participating in the occupational therapy and by later receiving education and vocational training he is creating for himself better chances of employment when he gets going again, and that thanks to the present chemotherapy he has good chances of recovery. In addition, the patient must understand that the time required for treatment will pass more pleasantly when he collaborates, planning his future while in the sanatorium. During this entire period it must be pointed out to the patient that medical treatment is most important but that at the same time he ought to utilise all the possibilities afforded by a long-term stay in sanatorium and hospital and by the convalescent period. In Denmark a disabled persons employment act has been passed. In accordance with this act several working clinics have been established, to which suited patients may be referred and where they can be occupied for some length of time. Their possibilities of working may be investigated, and a social worker is available for finding work for them. Sheltered workplaces have also been established: The National Tuberculosis Society owns two factories, one for steel tubes, This factory is intended for patients who are to receive vocational training and return to normal life. The patients are educated to the extent allowed by the type of work. Of course,

this makes this factory more expensive to run. The other factory employs mainly patients whose working capacity is so restricted that for a long time they must be expected to be able to manage work only in this factory. Here, more regard has to be paid to whether the work affords a reasonable income for the patients, less to the educational aspect. Unquestionably these factories have filled a gap. They spare many patients the bitter feeling of staying entirely inactive at home and introduce them, instead, gently into normal employment again.

Let me try to describe the efforts made in a tuberculosis sanatorium to make the patients understand that medical treatment is the most important factor of all, while at the same time they are given every chance of education and vocational training that can be afforded in a sanatorium or hospital. In my opinion, a tuberculous patient is better off if he does not come from the complete idleness of an old-fashioned sanatorium or hospital and has to start re-training after discharge. From the psychological point of view, occupational therapy gives the patients courage to face the future, it trains their abilities to re-enter normal life, and it prevents some of the unfortunate consequences of enforced idleness in a sanatorium.

In a tuberculosis hospital or sanatorium the patient must be told from the very outset that the stay is going to be prolonged. Despite modern therapeutic methods, the stay in hospital or sanatorium has not been greatly shortened.

The patients may be classified into three groups:

(1) Those who return, entirely fit, to their former work;

(2) Those whose former job now exceeds their physical strength;

(3) Those in whom the disease has resulted in *reduced* working capacity, either because the lungs have undergone change or because their function has been restricted by surgery.

It is very important to measure "the maximum breathing capacity" by determining the ventilation of the lungs during a given period and to measure "the vital capacity", since many patients, among others the operated patients, often possess little working capacity because of impaired pulmonary function. By way of example, there was a 28-year-old man who could yield only 21 % of the normal average of the same age and size. It is out of the question that such a man can manage at a workplace where physical work is required. He has now been educated for clerical work, where he is doing a good job. Similarly, there was a patient aged 62 — that is, of an age at which there is still some possibility of working — who had only 42 % of the normal average. From industrial work he was transferred to sedentary work.

When deciding the question of the disablement pension, it is important to determine the ventilation of the lungs, since otherwise it is impossible to obtain an exact standard of the possibilities for work.

At the Nakkebølle Sanatorium our procedure is as follows. The rehabilitation programme is in three groups: Occupational therapy, education, and vocational training.

In *occupational therapy* the patients learn to occupy themselves with sewing and the like. This work is supervised by the occupational therapist, who sees to that it is of good quality and in good taste, since otherwise it cannot give the patients the full pleasure.

As soon as the patients are able to and wish to they receive *education*. This comprises typing, bookkeeping and languages, supplemented by correspondence courses and self-tuition. This is applicable for those who will enter occupations such as clerical and other sedentary work. We have had this educational programme for many years and some of our patients have attained quite important independent positions. Let me mention a diver who now has a big clerical job and a labourer who is now payroll accountant in a big concern. These are people who took the education seriously from the very outset and who reached a high standard by means of correspondence courses and self-tuition. *Typing* is the most popular subject, sought by artisans, clerks and apprentices. *Bookkeeping* is in request by artisans for use in their businesses. *Languages* are also very popular, and a few patients have studied *Danish literature* and *Esperanto*.

In Denmark there is an association of tuberculous patients called "Boserup Minde", and this association grants economic support to correspondence courses which frequently conclude in a diploma.

The central library is of great assistance to the tuberculous patients. Here they can borrow technical literature, and the library includes a fairly comprehensive vocational card index, where the patients can seek information regarding their future work, both as to what work is to be had within the different branches and the economic possibilities in the work.

Self-tuition: There are always patients who prepare for matriculation in a university, and during the stay in the Sanatorium two patients passed the final secondary school examination of a "Realskole". Several have obtained their teacher's certificate or passed the entrance examination for a training college. These patients have been provided with a reading room where they can study undisturbed by the other patients, and where they can prepare their papers.

The actual *rehabilitation and vocational training* takes place in the workshops of the sanatorium, which have to be, like all the other arrangements, in charge of well educated instructors with paedagogic as well as technical qualifications for setting the patients going. It is very important

to choose the right instructors, because without suited instructors any rehabilitation and re-training is out of the question. The workshops are separated from the Sanatorium. This gives the patients a feeling that during the time they are occupied in the workshops they are doing a piece of work and receiving the education they need, while in the Sanatorium building we have the hobby room where they can occupy themselves with other things.

There is an *engineering workshop* where the patients learn to make hospital equipment, and a *joiner's shop* where they learn to make furniture of many different kinds, not only for our own use, but also for the tuberculosis centres. The patients *weave* and they *sew* uniforms and the like for various institutions. *Knitting* is popular, making sweaters, etc., for a number of children's institutions. In *gardening* we have built greenhouses, and we have fitted up a *poultry farm* and keep geese. After discharge many patients, though unable to take part in actual farming, can establish small poultry farms and at the same time weave. In this way they can utilise their working capacity and make a living.

In addition, we have given a number of Greenlandic patients *motor instruction*, which is very important to them, and a few patients with very restricted occupational possibilities have been taught *brush-making*. In Denmark the latter has been carried out mainly by blind people, but we have had patients who were unable to do anything else and they have made a small job out of brush-making. *Book-binding* has also been carried on.

The administrative aspect of this work is in the hands of the sanatorium manager, who constantly has to procure the orders which make it possible to run the workshops. This requires much preparation and thought, planning, and control of the quality of the work. If the workmanship is not satisfactory, the articles are not accepted for distribution. The patients are paid for their work, that is, they receive the price paid for the articles less the expenses of the Sanatorium. This has been soemwhat fluctuating, but now we have got so far that the rehabilitation work in the Sanatorium is run without the great loss which has prevented many places from starting such a programme. Still, the Sanatorium pays for the teaching and for the interest and depreciation on the buildings.

Last year, the turnover was 68,616 Danish kroner and 71 patients participated. At present, 34 out of the total of 92 patients are working at the rehabilitation workshops.

Such a programme cannot be started all at once. It has to develop gradually, and it is something which takes place towards the end of the patient's stay. It requires a favourable attitude on the part of *everyone:* physicians, nurses, and administrative staff. If not, the patient will lose

interest. To our great surprise, however, the patients have been very keen, and apparently they have never felt they were working for the Sanatorium. On the contrary, they have understood that the work they were doing was being estimated in a fair way and that they were receiving their share, and that they were learning something from which they would benefit after leaving the Sanatorium. While at first we had expected that 15 per cent of the patients would take part in the actual rehabilitation programme, we have had as many as 40—50 per cent. Of course, it must be emphasised again that the medical treatment is the most important part of the regime, and that the rehabilitation has to be run in a way so as to support and never to interfere with the actual treatment.

After leaving the Sanatorium the patients are referred to vocational guidance centres for handicapped persons established all over Denmark, but this is the subject of Dr. Isager's paper.

It is to be hoped that this programme, which has been in operation for a number of years and which has proved, at follow-up, to have been of great benefit to the patients, will now form a natural link in the sanatorium treatment, so that the patients do not feel that staying at a sanatorium is tantamount to spiritual and occupational death.

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FROM THE CENTRAL COUNTY HOSPITAL OF AALBORG,
CHIEF: KARSTEN ISAGER, M.D.

REHABILITATION OF DISABLED PERSONS IN THE CITY AND COUNTY OF AALBORG, DENMARK

By

KARSTEN ISAGER

In his paper on the rehabilitation of the tuberculous in Denmark, Dr. Helms described the organisation of this programme in one of our biggest sanatoria.

It is now my turn to report how rehabilitation of tuberculous patients discharged from hospitals or sanatoria is organised in a Danish county, the county of Aalborg which has a population of 225,885.

Only 8—10 years ago the prognosis of pulmonary tuberculosis, *quo ad vitam* as well as *quo ad valetudinem,* was so grave that only a small percentage of the patients returned to their previous jobs, healthy and fit for work. In those days the risk of infection was one of the factors which involved great, often unreasonable, difficulties in finding suitable employment for the ex-patient.

Owing to the recent great advances in respect to the curability of tuberculosis, it is a fact that most of our patients are sputum negative when discharged from hospital or sanatorium. After termination of treatment a large number of these patients can return to the job they had before the onset of their disease. This applies not only to self-employed persons, but also to a large number of those who are employed in public institutions or in private concerns, both of which show understanding and readiness to help those who have been ill.

Even now, the treatment of tuberculosis often takes a long time before the patient can be said to be healthy and fit for work. Moreover, surgical therapy may have reduced pulmonary function and this involves a risk of cor pulmonale. The patients need vocational training and re-education, and since most tuberculous patients on leaving the hospital or sanatorium are now stabilised (i.e., definitely sputum negative), they can be trained and re-educated together with patients disabled by other diseases. This contributes to relieving the tuberculous patients of the feeling of isolation which from olden times has attached to having or having had tuberculosis.

We are on our way to do entirely away with the misunderstood fear of infection which previously made our patients lose courage.

The rehabilitation activities are now in the hands of the 19 public labour exchanges in Denmark. These exchanges have special sections for disabled persons, meaning persons for whom it is difficult to keep or obtain employment due to a physical, psychic, or social handicap.

The work is supervised by social workers assisted by a labour exchange officer and a vocational guidance expert in close collaboration with the public assistance offices and the disablement insurance court. It may be mentioned that during the one-year period 1954—55 there were 2,193 new applicants. In fiscal year 1955—56 the corresponding figure was 2,665, and in the subsequent years 2,480. Out of the latter number, 1,672 were men and 808 women. For the whole of Denmark the new applicants with pulmonary tuberculosis were 256, 296, and 304 during the years 1954—55, 1955—56, and 1956—57 respectively, and in the course of this 3-year period suitable employment was found for about half of them. Out of all 2,480 applicants in 1956—57, 1,158 could be placed in suitable employment: 1,044 in private concerns and 114 in more sheltered workplaces.

The section for disabled persons in Aalborg was established in 1952. That year it dealt with 56 applications and during the past year with 170 (129 men and 41 women). Tuberculous patients made up about 20 per cent. The figures from Aalborg show the same percentage of obtained employment as the figures for entire Denmark: Employment could be found for between 40 and 50 per cent within the first year. For the other half, vocational training and re-education take a much longer time. By way of example it may be mentioned that a former mechanic has gone through a secondary school course preparing for university matriculation and has later been educated as a librarian, and that a former labourer is now apprenticed to a painter. Due to the sequelae of surgical treatment, his pulmonary function is considerably reduced, so his working day is only 6 hours. This makes the duration of his apprenticeship longer than normal.

The Aalborg labour exchange has established a joiner's shop, a bookbinder's shop, and a dressmaker's shop employing 40 persons of both sexes.

At the Aalborg historical museum two disabled persons are engaged on restoration work, and in the nearby town of Hjørring a few persons are employed in the same type of work. For some years the municipality of Aalborg has been extending its parks, and between 60 and 70 persons have constant employment in laying out and maintaining the parks. Among the young rehabilitants several are referred for education in folk high schools and county colleges, and this affords an excellent opportunity

of forming an impression of their suitability for work. The exchange also has intimate collaboration with the technical school and the commercial school of Aalborg, and in finding suitable employment extensive use is made of psychotechnical tests.

It is worth mentioning also that on April 1, 1957, the Society for Disabled Persons established a so-called rehabilitation institute dealing primarily with patients suffering from orthopaedic diseases, but it receives also former tuberculous patients. At this institute the patients have possibilities of being educated as mechanics. On the advice of the technical school, the trainees first receive basic training for three months, and during this period they learn how to make the tools which they will need later. This affords a unique opportunity of forming an impression of whether the trainees are suited as mechanics. The basic course accommodates 6 trainees, and after 3 months' training they are sent out as apprentices in ordinary workshops or the continue their training in the machine or welding workshop of the institute, which accommodates 15 persons.

The institute also has a weaving school with room for 7 and a department where the pupils learn how to operate a knitting machine. Moreover, there are various forms of simpler needlework and applied art under the supervision of an occupational therapist.

During the first year that the institute has been in operation, 44 trainees have been accepted, and now employment has been found for 12 of them at ordinary workplaces. A few of the sections may be used as so-called sheltered workshops, but otherwise there are as yet no possibilities of employing severely and permanently disabled persons who can work for only a few hours a day. There is a great need for such sheltered workshops, where the work is primarily of psychological value. The muncipality of Aalborg is planning to establish 3 or 4 workshops of this type. This will be done in connection with the building of a new residential quarter for 10,000 inhabitants. In the centre of this quarter there will be a block of flats with communal ficitlities, 30 % of which are to be rented to disabled persons. A hostel is also being built for young people to live in while they are being educated in Aalborg, and its accommodation is to be divided equally between healthy and disabled persons.

This quarter will have its own school, church, and library, there will be nurseries, nursery schools, and shops. As time goes by, it will be attempted to assemble all rehabilitation activities in this quarter in order to facilitate the proplem of transport, which is of such great importance to disabled persons.

Lastly, it may be stated that rehabilitation activities are easiest to operate for persons living in towns, while great difficulties are connected

with finding suitable employment for persons in rural areas. During the years to come, rehabilitation efforts will have to tackle the question of moving disabled persons from rural areas to those towns where the facilities for organising rehabilitation programmes are at hand.

The sources of the figures mentioned in this paper are as follows:

1. Report on assignments of work and unemployment insurance, fiscal year 1956—57 (in Danish) Socialt tidsskrift, January 1958, vol. 34, No. 1.
2. Report on the activities of the Aalborg Rehabilitation Institute, fiscal year 1957—58 (in Danish).

OPERATION OF THE REHABILITATION DEPARTMENTS OF THE SATAKUNTA SANATORIUM

By

RISTO ELO

At the end of 1931 the Satakunta Sanatorium received as a donation (from farmer and Mrs. Antti V. Tarkki) an estate which, after being refitted, was opened at the end of the following year as the sanatorium's rehabilitation department. Work was begun there in January 1933.

The Tarkki rehabilitation department is open to women and accommodates 30 to 32 patients. Since the time of its opening under Professor Väinö Horelli, then chief physician, a regular and systematically conducted work therapy has been carried on, in addition to the general rehabilitation of patients. Patients are admitted who are considered to be able to work for one to four hours daily but who nevertheless are in need of continued care. It is the object of the rehabilitation department to determine the working ability of the patients before they are fully discharged from the sanatorium, and at the same time to train them in occupations suitable to them. The patients have attended to housecleaning, cooking and serving of food, care of small livestock, and partly also to the fruit and vegetable gardens on the farm. Instruction has been given in cooking, sewing, weaving, lacemaking and crocheting. For many years all the sewing, weaving and mending for the sanatorium was done at the Tarkki rehabilitation department.

In 1949 the Satakunta Sanatorium bought from the Finnish Anti-Tuberculosis League the Kauttua Sanatorium, from which it formed the Kauttua rehabilitation department for men, with 30 to 33 beds. All the patients have done the usual janitor's work, at the same time as courses have been arranged for them in wood-working, electrotechnics, automobile driving, and other occupations.

The total number of patients that can be accommodated in the two rehabilitation departments of the sanatorium is 60 to 65, which corresponds to the need as estimated by a special committee on rehabilitation

work. (The total number of beds in the Satakunta Sanatorium is 600). Accommodations have indeed been adequate. During the past few years there occasionally have been unoccupied beds in the women's department, since the number of female patients is decreasing. Furthermore, they appear to have less need of rehabilitation than the men, since the sanatorium receives its patients chiefly from rural areas, where household work is available for untrained female labour.

A total of 1,063 patients were discharged from Tarkki in the period 1933—1957, and 388 patients from Kauttua in 1949—1957. Their distribution according to sex and age is shown in Table 1.

TABLE 1

Number and age of patients discharged from rehabilitation departments

	11—15	16—20	21—25	26—30	31—35	36—40	41—45	46—50	Total
Tarkki 1933—57									
Female	51	289	260	146	98	45	45	45	979
Male	7	27	22	13	5	4	5	1	84
Total Tarkki ..	58	316	282	159	103	49	50	46	1063
		├——	860	——┤					
Kauttua 1949—57									
Male	69	116	68	50	24	17	14	14	372
Female	3	7	4	—	—	2	—	—	16
Total Kauttua .	72	123	72	50	24	19	14	14	388
		├——	269	——┤					
Total T & K ...	130	439	354	209	127	68	64	60	1451

As is seen from this table, the age group 16—35 years included 860 patients (80.9 per cent) at Tarkki and 269 patients (69.3 per cent) at Kauttua, or a total of 1,129 patients (77.7 per cent). Accordingly, the Satakunta Sanatorium has been able to give rehabilitation training to patients of the age at which the importance of such training is greatest. Two or three male patients at a time have served as janitors at the women's rehabilitation department at Tarkki, while the female patients at Kauttua remained there after it was discontinued to be used as a sanatorium.

The follow-up therapy of a patient with tuberculosis is greatly influenced by his social status and the possibilities of work that it offers. Rehabilitation and the learning of a new trade is most important for persons who previously were occupied in heavy manual labour. The patients at Tarkki and Kauttua had previously had the occupations shown in Table 2.

TABLE 2

Occupation of discharged patients or of their families

	Farm and forest labourer	Common labourer	Factory worker	Building worker	Free profession	Trade and traffic	Agriculture	House maid
Tarkki 1933—1957	323	342	111	—	32	108	—	147
Kauttua 1949—1957	117	89	70	21	52	22	17	—
Total	440	431	181	21	84	130	17	147

The great majority of the patients (1,052) were farm and forest labourers and industrial workers, whose work in most cases is heaviest, whereas the number of independent farmers was low. Among women there was a relatively large number of housemaids (147), most of whose work in farm households was heavy.

It was considered to be important to transfer to the rehabilitation departments the patients whose disease was cured or nearly cured but who still were in need of continued treatment. A distribution of the patients at Tarkki and Kauttua according to diagnosis is shown in Table 3.

TABLE 3

Diagnosis of patients discharged from rehabilitation departments

Diagnosis	Kauttua	Tarkki	Total
Tub. pulm.: min.	143	382	525*)
advanced	132	320	452*)
far advanced	61	177	238
St. p. resectionem seu pulmonectomiam ..	7	9	16
Resid. pleuritim exsud.	21	54	75
Tub. ossis variorum	13	54	67
„ lymphonodori variorum	7	27	34
„ cutis	—	29	29
„ organ. variorum	4	11	15
Total	388	1063	1451

*) Includes 347 patients then or previously with pneumothorax and 65 patients who had undergone thoracoplasty.

A large proportion of the patients (977) belonged to the groups of tub. pulm. min. or adv., for whom rehabilitation was considered to be important. The large number of advanced cases of pulmonary tuberculosis was due in part to wartime conditions and in part to the circumstance that severely ill patients were at first hospitalised in the Kauttua department. Importance was also placed on rehabilitation of patients with tuberculosis of the bone, consisting of spinal tuberculosis in a large proportion of cases. The rehabilitation of patients with pleuritis exsudativa was held to be necessary in order to prevent later complications (according to hospital records, no other form of tuberculosis has been diagnosed later in these patients). The care of tuberculosis of the skin was originally partly centred in the Satakunta Sanatorium, which accounts for the large number of these cases. Their transfer to Tarkki for the period of convalescence is comprehensible already because of the external symptoms.

Back to the sanatorium were transferred 46 patients (4.3 per cent) from Tarkki and 48 patients (12.4 per cent) from Kauttua, which, as was mentioned above, was originally a sanatorium.

As difficult as is the evaluation of the course of tuberculosis, a review of the results of treatment is made in Table 4.

TABLE 4

Result of treatment of patients discharged from rehabilitation departments

	Improved	Unchanged or poorer	Dead
Tarkki	918	142	3
Kauttua	315	71	2
Total	1233	213	5

During treatment at Tarkki, the condition of 13.5 per cent of the patients remained unchanged or became poorer; the corresponding figure for Kauttua was 18.2 per cent. The causes of the five deaths were acute pneumonia, far advanced pulmonary tuberculosis (2), myocardial infarction, and suicide.

During the period 1953—1957 the operation of both departments was changed in the respect that main emphasis is now being given to actual training courses, with less attention to hobby work. The courses are subject to the official inspection of the Government Board of Agriculture, and on completion of a course the patients receive certificates testifying the degree of training obtained.

It has been the aim to give as effective instruction as possible, and no alleviation has been made in the standard requirements of the courses. Patients unable to keep up with the course have had to drop out. The object is that a patient receiving a certificate will be able to do the work indicated by it.

The classes are held in the forenoon and the afternoon, separated by a rest period. There is no charge to the patient for treatment or instruction during the course.

The following training courses have been held at the Tarkki rehabilitation department:

	No. of Courses	No. of Participants
Hand-loom weaving (1953—1954)	3	36
Embroidery and hemstitching (1953—1954	2	34
Bobbin lace making (1953—1954)	3	33
Women's handicraft school (weaving and sewing) (1954—1955)	2	35
Dressmaking (1956—1957)	4	65
Total number of participants		203

The courses in hand-loom weaving were found to be less serviceable and also were less popular, since the craft now longer is lucrative. The handicraft school courses lasted 8—9 months and were too long for women. During the past two years, the only courses held have been dressmaking courses lasting about 4 months, with the object that the patients will be able to sew simple clothing for themselves and their families and to do ordinary mending. After this preliminary course the patient has an opportunity to attend a continuation course, which will give her sufficient skill to do dressmaking for clients. The first continuation course was held in the spring of 1958.

At the Kauttua rehabilitation department the following courses for men were organised in 1953—1957:

	No. of Participants
Automobile driver's school: professional	16
(private	6)
Painter's course	10
Wood-working course (men's handicraft school) for carpentry and surface treatment of wood	54
Total number of participants	86

The length of the driver's course and painter's course was about 4 months and of the wood-working course 8—9 months. This longer course has been found to be suitable for men. A course in metal work was started in the beginning of 1958.

In selecting patients for the courses attention was paid to their age. The distribution by age is shown in Table 5.

TABLE 5

Age of patients attending rehabilitation courses

	16—20	21—25	26—30	31—35	36—40	41—45	Total
Tarkki 1953—1957	31	27	26	19	8	9	120*)
Kauttua 1953—1957	15	28	20	9	9	5	86
Total	46	55	46	28	17	14	206

*) Some patients at Tarkki attended several courses.

A total of 175 patients (85 per cent) were 16—35 years old and therefore in the best age for instruction. It should be noted, however, that there were 31 patients over 36 years of age. The rehabilitation of these older age groups appears to be a difficult problem, since the most receptive age is practically over. It is also to be remembered that the older age groups of patients with tuberculosis are increasing in size, and this should be taken into consideration in drawing up the general plans for rehabilitation work.

For attendance at the courses, selection was made chiefly among

TABLE 6

Diagnosis of patients attending rehabilitation courses

Diagnosis	Kauttua	Tarkki	Total
Tub. pulm.: min.	44	58	102*)
advanced	33	33	66*)
far advanced	3	2	5
St. p. ectomiam seu pulmonectomiam ..	—	2	2
Resid. p. pleuritim exsud.	1	1	2
Tub. ossis variorum	4	19	23
„ lymphonodori variorum	1	1	2
„ org. variorum	—	4	4
Total	86	120	206

*) Includes 40 patients then or previously with pneumothorax and 23 patients who had undergone thoracoplasty.

patients with tub. pulm. min. and adv. and among suitable cases of tuberculosis of the bone. The patients attending the courses were distributed by diagnosis as follows:

A great proportion of the patients belonged to the tub. pulm. min. and adv. groups, and there were only 5 far advanced cases. The fact that the sanatorium has a department of its own for tub. ossis accounts for the high number of patients with this disease (23).

A distribution by occupation of the patients attending the courses is shown in Table 7.

TABLE 7

Occupation of patients attending courses or of their families

	Farm and forest labourer	Common labourer	Factory worker	Building worker	Free profession	Trade and traffic	House maid	Agriculture	Total
Tarkki ...	25	28	10	1	18	9	17	12	120
Kauttua .	14	29	21	5	10	5	—	2	86
Total	39	57	31	6	28	14	17	14	206

Most of the patients who attended the courses belonged to occupational groups doing heavy manual labour (farm and forest work, common labour, factory work) and therefore had no occupational skill.

In 1957 it was possible to begin on a small scale to study patients with a view to the selection of an occupation. This was done in part at the sanatorium and in part at the rehabilitation departments. Testing for suitability for various occupations was carried out at the Tarkki and Kauttua departments on 22 patients, and on the basis of the study it was possible to recommend to them certain occupational schools in line with their capacities and inclinations. When the patient then applied for entrance to a trade school the results of the test were already available. Additionally, a confidential report was prepared during his attendance at the rehabilitation course and was transmitted to the principal of the trade school to which he was applying.

The purpose of the rehabilitation courses is to give preliminary instruction for a suitable occupation and at the same time to give the patient an opportunity to improve his health, so that also those who do not intend to continue at a trade school will be able to manage better in other work. A follow-up inquiry concerning the benefit derived by the patients from these courses gave the following data:

Tarkki (120 participants):

— Employed by commercial concerns in seving	12
— „ „ „ „ „ other work	4
— In addition to her household work, sews clothes for self and family	39
— Doses outside sewing at home	20
— Attends continuation course in a trade school	17
— Has interrupted the course	5
— Is under sanatorium care	5
— Address not known	2
— No information	16
Total number of participants	120

It may thus be said that a large proportion of the patients who attended the courses at Tarkki are able to sew their own and their families clothing, which also is a socially significant factor. In addition, 20 women are capable of sewing for clients.

Seventeen patients have attended occupational schools for the disabled, i.e., business schools, a gardening school, and the school for disabled women in which training is obtained in dressmaking or hand-loom weaving. Sixteen patients were in employment, including 12 who were employed in sewing in commercial concerns. Nearly all the patients have stated that they are satisfied with the courses, only five declaring dissatisfaction. One of the latter had failed to finish the course and was of the opinion that it was useless since, for example, pattern drawing was taught!

Kauttua (excluding persons who had obtained a private driving license):

— Professional automobile driver's school:	
Working in this trade	7
„ „ other trades	3
No information	3
	16
— Painter's course:	
Working in this trade	3
„ „ other trades	3
Attending continuation course	1
Relapse of disease	2
No information	1
	10
— Wood-working course:	
Working in this trade	7
„ „ other trades	16
Attending condition course	25
Relapse of disease	6
	54

Thus, of a total of 80 patients who had attended a preliminary vocational course, 17 were occupied in the trade in which he had received instruction and 34 were working in other trades but had had a welcome period of recuperation while attending the course. A total of 17 patients had obtained further training by continuing at a vocational school for the disabled, i.e., in wood-working schools but also a part in metal-working schools, gardening schools and business schools.

To summarize, it may be said that the courses arranged in the rehabilitation departments have proved beneficial in working towards the rehabilitation of the patients. A considerable proportion of the patients have been able, after attending the course, to improve their livelihood and a large number have been able to continue their training in vocational schools in order to learn a new trade. Those who are continuing at their former or some other non-skilled field of work have during the courses learned the working habit once more, at the same time as their state of health was under supervision.

The personal study of patients for their suitability for various occupations has also proved to be an important step in the ultimate rehabilitation of patients leaving the tuberculosis sanatoria.

DAS ERGEBNIS ARBEITSPFLEGERISCHER MASSNAHMEN FÜR TBC-KRANKE. EINE NACHUNTERSUCHUNG AN HAND DES MATERIALS EINER 10-JAHRESPERIODE AUS DEM REGIERUNGSBEZIRK VÄSTERBOTTEN IN SCHWEDEN.[1]

Von

Malin Larsson und L. E. Warfvinge

Zusammenfassung: Von den 2333 Tbc-kranken, welche während der 10-Jahresperiode 1946—55 im Västerbottens Läns Sanatorium in Hällnäs zum ersten Male betreut wurden, waren 1284 (= 56 %) Gegenstand irgendeiner Form arbeitspflegerischer Betreuung.

Für die grösste Gruppe von 935 Personen handelte es sich lediglich um Arbeitsbeschaffung auf dem offenen Arbeitsmarkt oder in geschützter Beschäftigung. Für 100 Personen wurde eine Umplacierung für notwendig erachtet und für 249 eine Umschulung auf einen anderen Beruf vorgenommen.

Eine unerwartet hohe Recidivfrequenz von 19 % zeigte sich bei den Umgeschulten, während sie bei den Umplacierten erwartungsgemäss wesentlich höher lag, nämlich bei 31 %. Das Resultat ist Ausdruck für die Schwierigkeit, geeignete Arbeitsplätze für Tbc-kranke zu finden. Es zeigt aber auch, dass die Umschulung der Umplacierung als recidivvorbeugende Massnahme überlegen ist, und gilt dies besonders für die Lungenkranken eines nordschwedischen Bezirks mit gering differenziertem Erwerbsleben.

Als Beiprodukt der Untersuchung ergab sich die Feststellung, dass 13 % der Umgeschulten ihre frühere Arbeit — für die Mehrzahl war das Waldarbeit — wieder aufgenommen hatten.

[1] Der Originalvortrag wird in dem Periodicum "Kvartalsskrift för Svenska Nationalföreningen mot Tuberkulos" publiziert.

LUNG FUNCTION BEFORE AND AFTER PLEURECTOMY

By

NILS SVANBORG

The author had found in the literature very small and conflicting series of pleurectomised patients and the general opinion appeared to be that this surgical procedure is indicated in cases with insignificant or no changes in the parenchyma. The author explained the follow-up examination of patients pleurectomised in the St. Göran's Hospital, Stockholm. The first 20 cases were examined by spirometry and bronchospirometry before and after the operation. The function of the operated lung was improved in all cases, also in those in which resection or thoracoplasty was performed at the same time. No definite correlation was observed between the degree of lung changes and improvement of function. All the patients reported subjective improvement, which was not clearly correlated to the objective function measurements. The author expressed the opinion that the benefit from pleurectomy appears to be greater than is shown by the literature and that the significance of the operation possibly may also be higher than indicated by the results of the spirometric and bronchospirometric examinations. (Editor's abstract.)

FROM MJÖLBOLLSTAD SANATORIUM, FINLAND,
CHIEF: NILS RISKA, M.D., DOC.

BRONCHOSPIROMETRIC REGISTRATION OF THE FUNCTION OF THE LESS VENTILATING LUNG DURING EXERCISE

By

N. Riska and T.-L. Sellergren

When the function of one of the lungs is markedly reduced due to intrapulmonary or pleural processes, it is of great importance — especially before surgery — to study the function of each lung separately by bronchospirometry. The oxygen uptake is the best exponent of the lung's functional capacity, but the ventilation gives complementary information. Bronchospirometry is as a rule performed at rest. However, in many cases, there is reason to suppose that partial insufficiency, which is allayable by exercise, may be present in the less ventilating lung. In these instances, a more correct picture of the function of the lung is no doubt obtained if bronchospirometry is performed in association with ergometry.

In 1951, Björkman and Carlens studied about twenty patients by these means. They arrived at the surprising result that the percentile value for oxygen uptake remained unchanged in both lungs when the oxygen consumption increased due to exercise. These results were not, however, completely verified in our tests with bronchospirometry in connection with exercise.

Our investigation comprises seventeen patients performing graduated, mild to moderate physical exercise in connection with bronchospirometry by Carlens's catheter. The degree of exercise was adapted to suit the test person's physical condition. Mild exercise in our tests was between 150 and 300 kgm/min. and moderate exercise 400 to 750 kgm/min. The exercise was performed by cycle ergometry in recumbent position. In the cases of all the persons examined, resection treatment was contemplated, and as accurate knowledge of the function of the less ventilating lung was thus of great significance. For the less ventilating lung, spirometry at rest recorded values between 0 and 35 per cent of the total oxygen uptake, and between 0 and 45 per cent of the total ventilation.

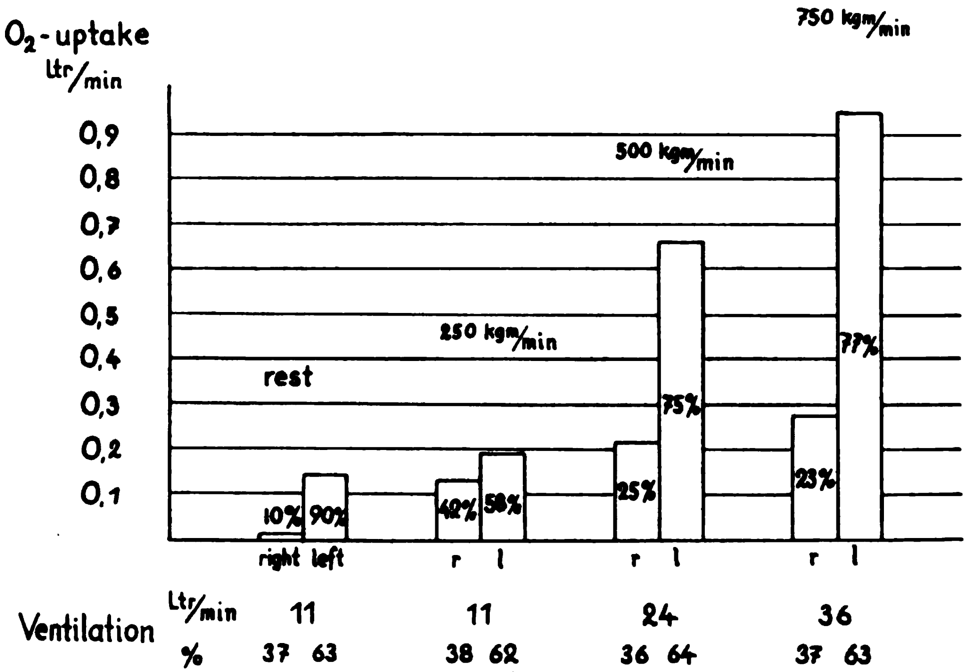

Fig 1.

Figure 1 shows the influence of physical exercise on ventilation and uptake of oxygen in each lung of a 52-year-old man in rather good physical condition but suffering from circulatory disturbances and incipient chronic pulmonary heart disease (cor pulmonale chronicum). At rest, the oxygen consumption of the right lung was 10 per cent of the total value, or 0.015 litres. Exercise of 250 kgm/min. did not cause increased ventilation, but very considerable augmentation of the oxygen uptake in the less ventilating lung: up to 42 per cent, or 0.135 litres/min. At 500 kgm/min. ventilation was doubled and the absolute oxygen consumption rose further but decreased relatively to 25 per cent of the total consumption. At 750 kgm/min. the ventilation was more than threefold, and the oxygen consumption of the less ventilating lung had risen to 0.28 litres, or more than the total oxygen consumption at rest. The relationship between the oxygen uptake of the right and left lung was the same as at 500 kgm/min. In all physical exercise tests, the mutual relationship between the lungs with respect to ventilation was the same as at rest. The absolute and relative increase in oxygen consumption of the

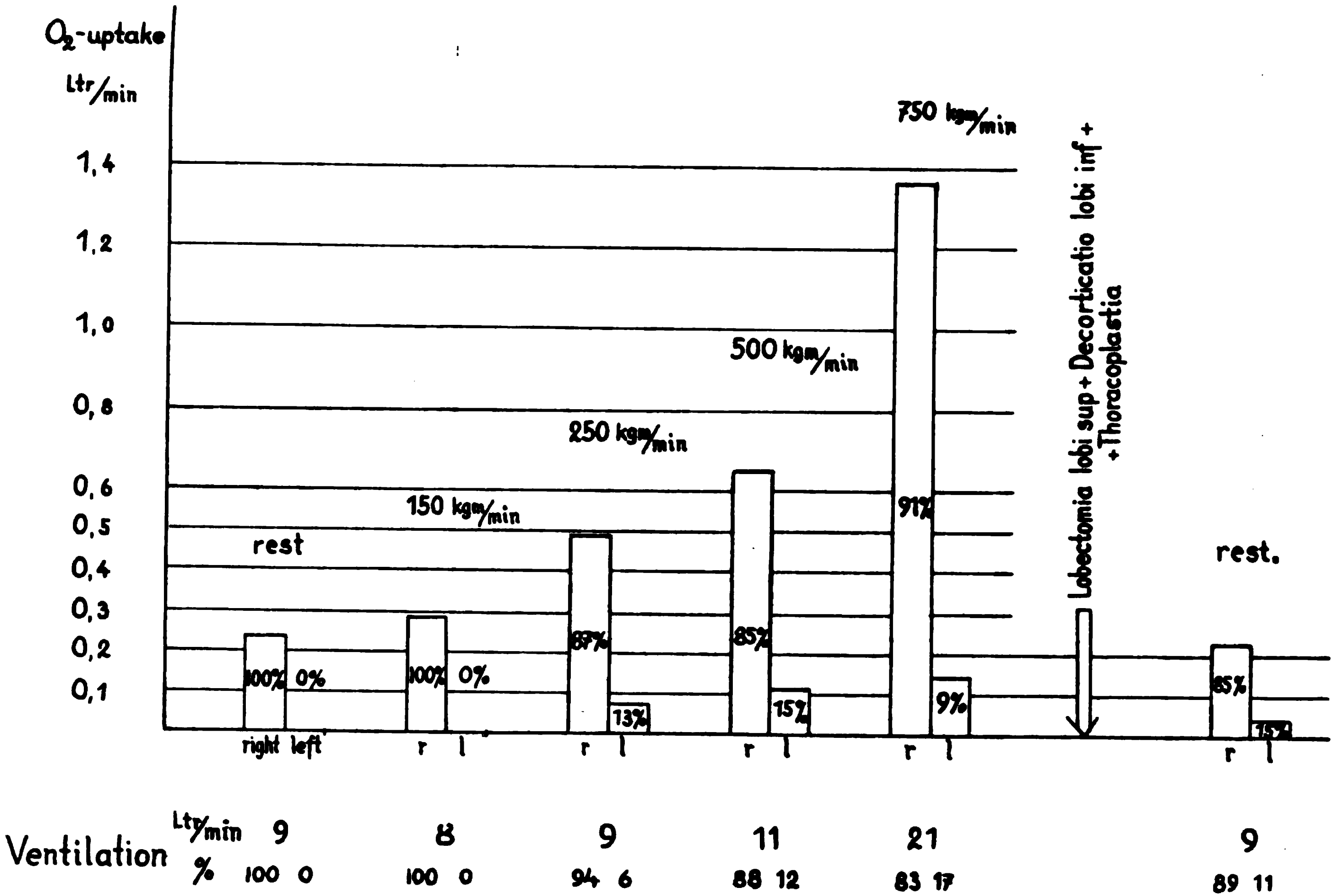
O2-uptake
Ltr/min
1,4
1,2
1,0
0,8
0,6
0,5
0,4
0,3
0,2
0,1
rest
150 kgm/min
250 kgm/min
500 kgm/min
750 kgm/min
Lobectomia lobi sup + Decorticatio lobi inf +
+ Thoracoplastia
rest.
100% 0%
100% 0%
87% 13%
85% 15%
91% 9%
85% 15%
right left
r l
Ventilation
Ltr/min 9 8 9 11 21 9
% 100 0 100 0 94 6 88 12 83 17 89 11

Fig 2

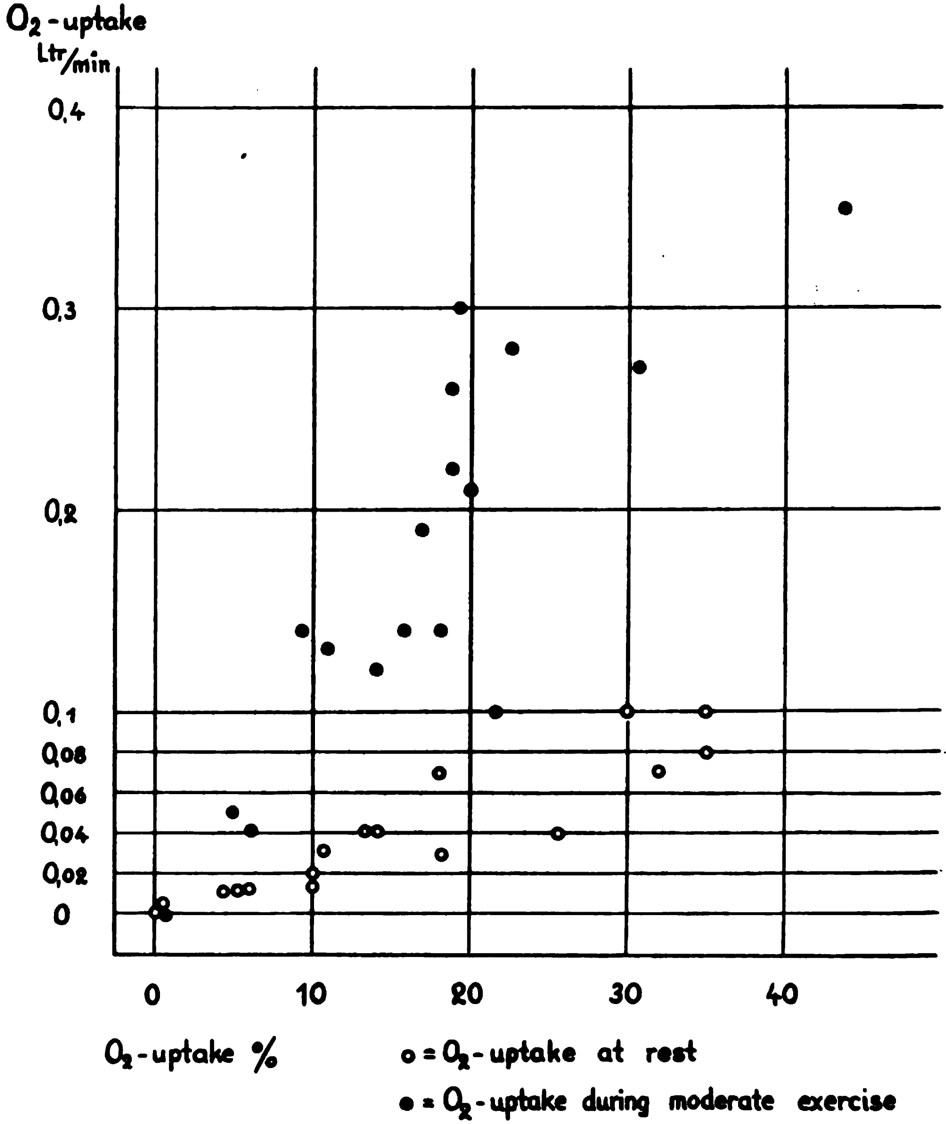

Fig 3

right lung noted in connection with the mildest strain, 250 kgm/min., was evidently due to an increased minute volume and enlarged capillary bed in the lungs, i.e., a circulation factor. The non-appearance of an increase in ventilation is another point in favour of this assumption. In the following tests connected with strain, increased ventilation was required to provide the oxygen supply needed. This series of tests with strain

shows that the function of the right lung should be given higher values than indicated by the oxygen consumption at rest, 0,015 litres or 10 per cent.

Figure 2 illustrates the oxygen consumption and its distribution in the right and the left lung of a 34-year-old woman who had earlier been treated by left extrapleural pneumothorax. The left lung did not ventilate at rest, nor in connection with exercise of 150 kgm/min. At 250 kgm/min. a certain ventilation and oxygen uptake was observed in the left lung, and at 500 kgm/min. the oxygen consumption of the less ventilating lung was 15 per cent of the total amount. At 750 kgm/min. the oxygen consumption in the left lung rose to 0.14 litres/min. but the relative value decreased to 9 per cent. Thus, by means of bronchospirometry and ergometry combined, it was shown that respiratory function of the less ventilating lung was possible. This was verified by bronchospirometry at rest performed after a surgical operation comprising lobectomy, plasty and decortication.

Figure 3 shows the oxygen consumption of the less ventilating lung at rest and during exercise. The ordinate is the absolute value in litres and the abscissa the relative value. In most instances the patient was capable of increased oxygen uptake when the oxygen requirement was increased. This did not mean, however, that the share of the less ventilating lung in the whole oxygen consumption was increased, although this was

TABLE 1

Effect of exercise on the O_2 uptake in the less ventilating lung

	Mild Exercise Compared with Rest	Moderate Exercise Compared with Mild
ABSOLUTE NUMBERS		
Improved	15	12
Unchanged	1	1
Diminished	—	—
0	1	1
Total	17	14
RELATIVE NUMBERS		
Improved	8	3
Unchanged	4	8
Diminished	4	2
0	1	1
Total	17	14

the case in about half the patients. Of the seventeen persons tested (Table 1), fifteen showed improved oxygen uptake in connection with mild exercise, and in association with moderate exercise the oxygen uptake rose furthermore in twelve out of fourteen persons. But the relative value rose only in eight instances, and further improvement at increased strain occurred in three only. When mild exercise was performed, the relative value remained unchanged in four cases, and when the exercise was increased, the relative value remained on the same level in eight of the person tested. In four the relative value registered was decreased.

A functional reserve is often registered by bronchospirometry in association with ergometry. This functional reserve is emptied at an early stage, and when the oxygen requirement is further increased the better lung increases its function more than does the poorer one. However, it is quite evident that in the cases described the less ventilating lung had a distinct mission to fill and that its functional share was of greater significance than indicated by the bronchospirometry performed at rest.

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FROM THE DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF TURKU (CHIEF: PROFESSOR AIMO PEKKARINEN, M.D.), SATAKUNTA SANATORIUM (CHIEF: DOCENT RISTO ELO, M.D.) AND PIKONLINNA SANATORIUM (CHIEF: DR. KALEVI LYYTIKÄINEN, M.D.)

ON THE ADRENOCORTICAL RESERVE IN CHRONIC TUBERCULOSIS

By

AIMO PEKKARINEN, KALEVI LYYTIKÄINEN and MARTTI TURUNEN

The organism often needs a hormonal defence mechanism. The changes in the tissues caused by the tuberculous infection and the reduction of lung function may lead to a homeostatic disturbance. In chronic tuberculous infection, bacterial toxins and febrile periods may influence the adrenal function. Some clinical symptoms of tuberculosis also may resemble Addison's diseace, e.g., weight loss and fatigue during the active stage of tuberculosis. The excretion of 17-ketosteroids and free 17-oxysteroids into the urine is often low in patients with chronic pulmonary tuberculosis who simultaneously have an increased sedimentation rate, hypotension, weight loss, persistent fever, and extensive changes in the lungs (Bastenie and Kowalewski, 1950; De Figueroa Taboda, 1950; Coldzieher and Edlin, 1953; Clarke, Zahn and Holmes, 1954). Febrile patients with cavitation and in an acute stage of the disease often give positive Keplers and Cutler-Power-Wilder tests (Pfeffer, Scherer and Staudinger, 1951). In patients suffering from serious lung tuberculosis with a poor prognosis there is an abundant excretion of sodium chloride into the urine on the second and third day during a Cutler test (Pfeffer *et al.*, 1951) and they often may also have a symptomatic hyponatraemia (Sims, Welt, Orloff and Weidham, 1950).

The resistance of the organism to infections is weakened in Addison's disease and also in the case of prolonged cortisone treatment, and in Cushing's disease, without chemotherapeutic protection.

In the chemotherapy of tuberculosis, prednisone and cortisone sometimes has a favourable effect on the treatment (Houghton, 1954; Johnson and Davey, 1954; Cochran, Hislop and Clayson, 1956; Alegria 1957; Crofton 1958; Wissler, 1958; Dahlström and Uggla, 1958). It may improve the general condition of the patient and it may decrease toxic, allergic and inflammatory reactions of the disease, the size of the lymphatic

glands as well as the mucus secretion in infections (Germuth, 1956). On the other hand, a prolonged cortisone treatment without chemotherapy may lead to spreading of the infection. Cortisone can also protect the test animal against the lethal effect of the bacterial endotoxin (Spink and Anderson, 1954); on the other hand, adrenalectomised test animals are very little resistant against endotoxin (Hallberg and Spink, 1955; Hallberg, Spink and Bittner, 1956). Some endotoxins may stimulate the adrenocortical function even equally efficiently as ACTH (Melby, Engdahl and Spink, 1957).

It might be important to know the adrenal function also in an evaluation of the indications for the surgical treatment of tuberculosis in order to be able, as accurately as possible, to estimate in advance, e.g., the surgical prognosis and the hormonal protection for operation that may be needed. In connection with lung operations we have earlier measured the adrenocortical excretion of middle-aged patients with pulmonary tuberculosis cortical excretion of middle-aged patients with pulmonary tuberculosis. After operation the total 17-OHCS excretion in the urine increased for 1—3 days (Halme, Pekkarinen and Turunen, 1957) and the number of eosinophil cells in the blood decreased (Pekkarinen and Turunen, 1955) on the first two postoperative days by more than 90 and 70 per cent respectively. These two reactions looked like reflections of each other. The content of free 17-OHCS increased in the plasma after lung operation (Viikari and Thomasson, 1957).

MATERIAL AND METHODS

The adrenal function was studied in 104 patients with a long history of active pulmonary tuberculosis. A total of 113 tests were performed, including the same test twice in 9 patients. Of the patients 69 were men and 35 women. Their average age was 40.6 years. The patients were chosen from two tuberculosis sanatoriums, which together had 1000 beds. The majority of them represented the most serious and chronic stage of the disease as to duration, type, extent and clinical condition. According to Forsman's and Larmola's grouping (1944), 35 patients belonged to the group stage II and 69 patients to stage III, which was the most serious one. 93 had one or several cavities in lungs. The average duration of the lung tuberculosis was 8 years. Thoracoplasty had been performed earlier in 21 patients, lung resection in 7, pneumothorax treatment in 26 patients, in 6 of these in both lungs, and pneumolysis in one patient. All the patients had received ample specific medical treatment for tuberculosis also during the ACTH test. Of the patients 28 were subfebrile, 8 had albuminuria, 5 tuberculosis in other organs, 3 empyema, 2 asthma, and 1 diabetes (Table 1).

TABLE 1

Some Characteristics of Patients with Lung Tuberculosis

	Number of Women	Number of Men	Total Number of Patients	Total Number of Analyses	Average Age, Years
	35	69	104	113	40.6

	Stage II Number of Patients	Stage III Number of Paitents
Subgroup A	20	65
Subgroup B	15	4

	Pneumothorax Number of Patients	Thoracoplasty Number of Patients	Resections Number of Patients	Pneumolysis Number of Patients
Earlier treatment	26	21	7	1

	Tuberculosis in Other Organs	Empyema of Pleura	Asthma	Diabetes
Number of complications	5	3	2	1

As the control, the basal excretion of the total 17-OHCS into the urine had been determined before the ACTH test. The adrenocortical reserve was determined by deep intramuscular injection of 80 units of depot-ACTH preparation (Cortrophine Z, Organon) on one day (40 units each at 8 a.m. and 8 p.m.) and by determining the excretion of total 17-hydroxycorticosteroids in the 24 hours' urine sample. The total 17-OHCS were determined by the method Jenkins et al. (Jenkins, Forsham, Laidlaw, Reddy, and Thorn, 1955). It was found that it was necessary to dilute the urine twice with water before the butanol exctraction to prevent the inhibition of the colour formation. Urine was saturated with sodium sulfate and extracted in butanol at pH 1. The colour reaction was performed on the butanol extract with the aid of the phenylhydrazine-sulphuric acid reaction, by keeping the samples in a thermostat at 50° for 45 minutes. The colour was read at the wavellength of 410 mu in a Beckman spectro-

photometer. The accuracy of the 17-OHCS method determined in recovery experiments with a hydrocortisone standard (20 μg/ml Leiras, Schering, Ciba), was 92.3 per cent with a standard deviation of 7.5 per cent. The preciston of the method calculated for the total 17-OHCS in the urine as the standard deviation of two independent dublicates are seen in the table 2.

TABLE 2

17-Hydroxycorticosteroids in the urine. The precision of the method calculated for the total 17-OHCS in the urine as the standard deviation of two independent dublicates.

17-OHCS mg per 1000 ml	S. D. per cent	Number of Analyses
2.4	30.0	354
6.8	16.8	326
12.0	11.6	243
22.6	10.8	404
36.8	5.4	170
52.4	3.9	70
68.6	2.8	58
112.2	6.5	34

RESULTS

Basal excretion of total 17-OHCS in the urine (Table 3)

The basal excretion of the total 17-hydroxicorticosteroids in the whole series averaged 3.8 mg. In the women the daily excretion was 4.2 mg and in the men 3.5 mg.

Excretion of total 17-OHCS during the ACTH day (Tables 3, 4)

During the depot-ACTH day the average excretion was 21.5 mg: for the men 20.9 mg and for the women 22.7 mg. Twenty-two of the patients had a more than normal excretion (above 30 mg) during the ACTH day; of them 9 had an excretion over 40 mg. The excretion was above the average, 21.5 mg, in a total of 54 patients and above 10 mg in 87 patients. An excretion of less than 10 mg occurred only in 17 patients. The majority of the patients had an excretion of 10—30 mg of 17-OHCS a day, which corresponds to a normal excretion in the intramuscular ACTH depot test.

Stage of chronic lung tuberculosis (Tables 3, 5)

Considering the degree of severity of the chronic tuberculosis of the lung there were relatively few patients whose adrenocortical excretion

TABLE 3

Urinary Excretion of Total 17-OHCS (mg per 24 hours) during Depot ACTH Stimulation and other Clinical Findings. Individual Cases.

Sex	Age, Years	Body Weight *)	Stage of Disease **)	Duration of Disease, Years	Total 17-OHCS: Basal Excretion, mg per 24 Hours	Total 17-OHCS: Excretion during ACTH Day, mg per 24 Hours	Urine Volume, ml/per 24 hours: Basal Excretion	Urine Volume, ml/per 24 hours: Excretion during ACTH Day	Drug, gm per 24 Hours
M	31	±	II	4½	15.0	68.0	2425	2000	PAS 14.0 INH 0.4
F	29	—	III	6	16.0	63.9	1900	4100	INH 0.3
F	31	±	III	6½	15.4	52.9	1750	1120	TSC 0.2
M	52	±	III	13	3.7	52.0	1150	1250	SM 1.0 PAS 12.0 INH 0.3
F	39	—	II	5	9.1	45.6	1600	1300	—
F	26	—	II	8	12.6	43.6	790	820	—
M	38	—	III	10	16.0	41.8	2350	1200	SM 1.0 PAS 12.0 INH 0.3
M	36	±	II	14½	0	41.7	1755	1835	SM 1.0 PAS 12.0 INH 0.3
M	51	—	II	6	2.0	40.3	2700	1600	PAS 12.0 INH 0.3
F	46	±	III	15	3.6	36.4	1600	2600	—
F	39	—	II	5	2.4	36.4	1900	1000	PAS 12.0 INH 0.3
M	54	±	III	30	0	36.3			—
M	43	—	III	5	2.0	36.3	2300	2250	PAS 10.0 INH 0.3
M	45	±	III	15	4.5	35.0	1500	1300	SM 1.0 PAS 12.0 INH 0.3
M	53	—	III	3	9.4	34.3		650	—
M	29	±	II	5	1.8	34.2	1025	500	—
M	38	—	II	17	0	34.0	1570	2000	—
F	19	±	II	10	0	33.0		1300	PAS 10.0 INH 0.3
M	49	±	III	3	0	32.4		2085	PAS 12.0 INH 0.3
M	29	±	III	5	7.4	32.0	1300	1100	SM 1.0 PAS 12.0
F	46	—	III	2	8.8	31.3	2200	1700	INH 0.3 PZA 1.5
M	27	±	III	4	0	31.2	1955	2000	—
M	43	±	III	5	6.9	31.0	2750	1300	—
M	55	±	II	9	0	30.8	1000	1100	INH 0.3 PZA 1.5
M	40	—	III	1	9.3	30.8	1800	1100	SM 1.0 PAS 12.0
M	50	—	III	14	1.6	30.5	2055	2060	PAS 12.0 INH 0.3
F	37	—	III	7	8.0	30.4	1000	1900	PAS 12.0 INH 0.3
M	45	±	III	10	0	29.4	2050	1470	SM 1.0 PAS 12.0 INH 0.3
M	50	—	III	13	1.7	29.2	1000	1000	SM 1.0 INH 0.3
F	48	—	II	3	8.2	28.9	2200	1125	INH 0.3 PZA 1.5
M	41	—	II	20	9.5	28.6	1700	1300	INH 0.3 PZA 1.5
M	50	—	III	6	20.2	28.6	1900	1700	INH 0.3 PZA 1.5
M	48	±	III	5	2.6	28.4	1638	850	SM 1.0 PAS 12.0 INH 0.3

*) — = length—100 —>10 kg
± = length—100 ± 10 kg
+ = length—100 + >10 kg

**) II ~ moderately advanced
III ~ far advanced

Sex	Age, Years	Body Weight	Stage of Disease	Duration of Disease, Years	Total 17-OHCS: Basal Excretion, mg per 24 Hours	Total 17-OHCS: Excretion during ACTH Day, mg per 24 Hours	Urine Volume, ml/per 24 hours: Basal Excretion	Urine Volume, ml/per 24 hours: Excretion during ACTH Day	Drug, gm per 24 Hours					
M	30	±	III	1	0	27.5	1660	1325	TSC	0.1				
M	40	+	II	10	8.8	26.4	1700	3000	PAS	12.0	CS	0.5		
M	50	—	II	5	0.8	25.7	1020	900			—			
F	47	—	III	16	7.2	25.7	1090	950			—			
M	29	±	III	5	6.8	25.5	1550	2000	PAS	12.0				
M	54	—	III	9	0	25.3	1800	1150	SM	1.0	PAS	12.0		
M	55	±	III	7	5.7	25.0	1100	1300	SM	1.0	PAS	12.0		
F	46	±	III	19	5.5	24.9	700	700	PAS	12.0	INH	0.3		
M	45	—	II	17	0	24.4	2550	1850	PAS	12.0	INH	0.3		
M	76	—	II	4	10.2	24.3			INH	0.3				
M	54	±	II	2	0	24.1	1800	1400			—			
F	36	±	II	10	2.4	24.1	1060	860	PAS	12.0	INH	0.3		
F	20	—	III	5	0	23.9	1200	1150			—			
F	50	—	II	2 ½	7.6	23.7	1200		CS	0.5				
M	47	—	III	5	3.6	23.7	1550	1380	PAS	12.0				
M	28	±	III	9	11.4	23.7	1500	1150	PAS	14.0	INH	0.4	VM	1.0
F	58	±	II	33	0	23.5	1650	1100	INH	0.3				
F	32	—	III	7	—	23.1		2100	PZA	0.5				
F	29	—	III	20	4.9	22.8	1410	1000			—			
F	35	—	II	6	0	22.2	2450	1500	PAS	10.0	INH	0.2		
F	26	—	III	10	—	22.0	1650	1500			—			
F	37	—	II	15	0.4	21.8	350	200	SM	1.0	PAS	10.0	INH	0.2
M	41	—	III	8	2.2	21.6	1540	1100	PAS	12.0	INH	0.3		
M	35	—	III	1	2.3	21.2	1565	900	PAS	12.0	INH	0.3		
M	56	—	III	5	2.1	21.0	1350	1010	PAS	12.0	PZA	1.5		
F	30	—	III	6	1.4	20.9	900	900	PAS	12.0				
F	29	—	II	13	—	20.3		1300	INH	0.3				
F	29	±	III	7	2.0	18.7	1250	1200	SM	1.0	PAS	12.0	INH	0.3
F	21	—	II	4	0	18.5	1250	1400			—			
M	64	±	II	5	0	18.2	1900	1300	PAS	12.0	CS	0.5		
F	38	—	III	5	1.3	18.0	900	450			—			
M	44	±	III	6	0.9	17.9	1240	1635	PAS	12.0	INH	0.3		
M	26	—	III	10	—	17.2	1143	1300	INH	0.3	VM	1.0		
M	29	—	III	5	8.3	16.2	750	800	SM	1.0	PAS	10.0	INH	0.3
M	21	—	III	4	0	16.1	1515	845	PAS	12.0	INH	0.3		
M	51	±	III	10	0	15.5	1000	900	PAS	12.0	CS	0.5		
M	38	—	III	16	1.8	15.2	2300	1200	INH	0.3	PZA	1.5		
F	56	±	III	4	1.8	15.2	1100	1000	CS	0.5				
F	22	—	II	5	1.9	15.0	1120	1500	CS	0.5				
M	50	—	III	6	4.9	15.0	1900	1000			—			

Sex	Age, Years	Body Weight	Stage of Disease	Duration of Disease, Years	Total 17-OHCS: Basal Excretion, mg per 24 Hours	Total 17-OHCS: Excretion during ACTH Day, mg per 24 Hours	Urine Volume, ml/per 24 hours: Basal Excretion	Urine Volume, ml/per 24 hours: Excretion during ACTH Day	Drug, gm per 24 Hours
M	63	—	II	4 ½	2.7	15.0	1800	1975	PAS 12.0 INH 0.3
M	48	+	II	3	2.8	15.0	1925	1250	—
M	28	+	III	10	6.2	15.0	975	1045	INH 0.3 PZA 1.5
M	37	±	II	9	8.6	14.8	1025	1800	SM 1.0 PAS 12.0
M	40	—	III	8	5.4	14.3	1800	1700	CS 0.5
M	30	—	III	5	—	14.2		1825	INH 0.3
M	37	—	III	12	0	14.2	2000	1700	CS 0.5
M	63	±	III	1	4.4	13.6	1375	1130	PAS 12.0 INH 0.3
M	43	±	III	1	—	13.2		3013	SM 1.0 PAS 12.0 INH 0.3
M	44	±	III	15	8.3	12.9	1500	1250	—
F	42	—	III	3 ½	5.2	12.8	1500	800	PAS 12.0 PZA 1.5
F	28	±	II	7	2.1	12.1	1400	750	—
M	28	+	II	11	2.7	12.1	2200	2000	—
F	29	—	III	2 ½	2.0	12.0	1300	600	PAS 10.0 INH 0.2
M	58	—	III	20	0	11.9	1300	900	CS 0.5
M	29	±	III	9	2.1	10.9	1050	1700	PZA 1.0
F	27	—	II	5	0	10.9	1540	1400	—
F	48	—	II	3	1.6	10.8	1350	1700	PAS 12.0 INH 0.3
M	30	±	III	3	0	10.8	2200	1800	PAS 12.0 INH 0.3
M	52	—	III	11	0	10.8	1300	1500	PAS 12.0 CS 0.5
M	54	±	III	30	1.3	10.8	1650	1000	—
M	45	±	II	5	0	9.5	1600	1350	TSC 0.15
M	43	±	III	1	—	9.0		1150	PAS 14.0 INH 0.3
F	30	±	II	3	3.4	8.2	1230	930	CS 0.5
F	26	—	III	10	0	7.8	1100		—
M	29	—	III	8	3.6	7.8	1800	1750	PAS 12.0 INH 0.3
M	23	±	III	8	7.4	7.7	2950	2450	PAS 14.0 INH 0.3
M	48	±	III	5	2.7	7.7	1810	1765	PAS 10.0 INH 0.3
M	34	—	III	13	5.6	7.5	1750	1100	PAS 12.0 INH 0.3
M	57	±	III	10	0	6.8	1750	2130	PAS 12.0 INH 0.3
M	59	±	III	6	0	6.2	1700	1100	CS 0.5
M	40	±	II	3	5.4	5.8	850	760	SM 1.0 PAS 12.0 INH 0.3
F	36	±	III	9 ½	1.3	5.8	900	900	—
M	60	—	III	2 ½	0	5.2	1525	675	PAS 12.0 INH 0.3
M	45	±	III	3 ½	0	4.4	2125	2000	PAS 12.0 INH 0.3
M	41	—	II	9	0	3.3	1700	2000	CS 0.5
M	38	+	III	11	0	3.0	1145		PAS 12.0 INH 0.3
F	31	±	II	9	5.6	2.6	1600	1700	CS 0.5
M	29	—	III	8	0	2.4	1005	1195	PAS 12.0
F	54	—	III	20	3.6	1.8	1320	1300	CS 0.5

TABLE 4

Urinary Excretion of Total 17-OHCS (mg per 24 Hours) during Depot ACTH Stimulation

ACTH Day, mg per 24 Hours	Number of Women	Number of Men	Total Number in Series	Per cent of Total Number
Over 50 mg	2	2	4	4
41—50 mg	2	3	5	5
31—40 mg	4	9	13	12
21—30 mg	12	20	32	31
11—20 mg	11	22	33	32
0—10 mg	4	13	17	16
Average	35	69	104	100

was low. The degree of severity of the disease was not correlated to the size of the adrenocortical excretion. In stage II the excretion of 17-OHCS in the urine during the ACTH day was 22.2 mg in subgroup A and 25.0 mg in subgroup B, and in stage III correspondingly 20.8 mg and 20.7 mg. The average excretion was not significantly lower in III than in II stage. The patients who excreted less than 10 mg of total 17-OHCS during the ACTH day belonged evenly to both stages of the disease and were also evenly distributed according to age and weight. Clear symptoms of adrenocortical insufficiency were not observed clinically in this group.

Effect of age (Tables 3, 6)

The adrenocortical reserve of the adrenals was on the average good also in old (above 50 years) tuberculous patients. Their excretion of total 17-OHCS was 20.2 mg during the ACTH day. In those who were more than 60 years of age (5 patients) the average excretion was then 15.3 mg per day. Those 31—40 years old had then the highest average excretion (24.2 mg). The differences between the age groups were small.

TABLE 5

Urinary Excretion of Total 17-OHCS (mg per 24 Hours) during Depot ACTH Stimulation in Different Stages of Lung Tuberculosis

	Stage II		Stage III	
	Mg per 24 Hours	Number of Patients	Mg per 24 Hours	Number of Patients
Subgroup A	22,2 mg	20	20.8	65
Subgroup B	25,0 mg	15	20.7	4

TABLE 6

Urinary Excretion of Total 17-OHCS (mg per 24 Hours) during Depot ACTH Stimulation. Effect of Age.

Age in Years	Number of Patients	Mg per 24 Hours
21—30	30	20.3
31—40	24	24.2
41—50	28	21.5
Over 50	22	20.2

Effect of weight (Table 7)

Per weight unit the excretion of total 17-OHCS was significantly greater in thin (0.38 mg/kg/day) than in obese patients (0.29 mg/kg/day); however also their ACTH dose was greater per weight unit, as all the patients were administered the same ACTH dose. With one exception the thin patients were bed patients, while all those that had overweight were allowed to walk about.

When examining the results from the point of weight groups we find that in very thin patients (= height — 100 — > 10 kg) the total excretion of total 17-OHCS per individual was on the average rather normal (21.4 mg). When the weight was = height — 100 (average weight 75 kg) the excretion in 62 patients averaged 21.7 mg, which corresponds to the normal excretion of the whole material.

Individual variations in the adrenal reserve

When the ACTH test was carried out in 9 patients twice at a 10 months' interval, the average excretions were 21.7 and 25.6 mg. In four cases the excretion was in both tests almost the same, and in one case it was low each time. In two cases it was low the first time and high the second time. In two other cases the excretion was within the normal ranges, but its variation was considerable.

TABLE 7

Urinary Excretion of Total 17-OHCS (mg per 24 Hours) during Depot ACTH Stimulation: Effect of Body Weight

	Number of Patients	Mg per 24 Hours
Patients of underweight	38	21.4
Patients of normal weight	62	21.7
Patients of overweight	4	14.1

DISCUSSION

When examining the correlation of the clinical state of the patients to the excretion of total 17-OHCS in the group of severe chronic pulmonary tuberculosis, the adrenocortical excretion had no clear correlation to the patient's weight, age, type or extent of the changes in the lungs, fever, or complications. The excretion of 17-OHCS could be relatively good although the patient was old, thin or had large changes in the lung. As the excretion in the group of very thin patients, also, was almost of the same size, it can be said that the body weight also had no clear influence upon the total excretion of 17-OHCS by the adrenals.

The average adrenocortical excretion of the total 17-OHCS was during the first ACTH day normal or a little above normal. The majority of chronic tuberculous patients have a sufficient adrenocortical function for illness of short duration, which a one-day ACTH test corresponds to. By an ACTH test we cannot, however, explain the ACTH reserve of the anterior pituitary gland which is necessary for the continuous regulation of the adrenal function. There also were patients who during the one day ACTH test had a low excretion. In these patients the excretion in a 2 days' ACTH test would show the insufficient adrenocortical function more accurately.

The excretion of total 17-OHCS increased in 38 tuberculous patients fairly well in connection with lung operations (Halme, Pekkarinen and Turunen, 1957). Their normal basal excretion of 5 mg before the operation rose during the first three postoperative days to, on the average, 19.5, 16.6 and 11.4 mg per 24 hours, respectively. The average excretion after lung operation was during the first day and second day almost the same as the corresponding excretion of the tuberculous patients in our series during an ACTH day. It is interesting to compare the adrenocortical excretion of 17-OHCS after lung surgery and after an ACTH test in tuberculous patients. The patients in our investigation of adrenocortical reserve in tuberculous patients, of whom the greater part were in stage III of tuberculosis, had a more serious stage of the disease than ordinary tuberculous patients from the point of view of the cardio-pulmonary function. They do not form a normal surgical material for lung tuberculosis. In the ACTH test the adrenocortical excretion of total 17-OHCS of the patients with chronic pulmonary tuberculosis was equally high in both men and women. On the other hand, the rise in the excretion after operation in ordinary tuberculous patients was much smaller in women than in men. A division according to sex could be observed also in patients with chronic rheumatoid arthritis in ACTH test (Pekkarinen and Kalliomäki, 1958). During three consecutive ACTH days the total 17-OHCS excretion of the men was then

about twice as high as that of the women. In men with chronic rheumatoid arthritis a corresponding reserve as in tuberculous patients could be noticed on the first day, but in women the excretion was 50 % smaller. This excretion was doubled on the second day, and on the third day it still increased by about 2/3 of its second ACTH day level.

It would have been interesting to examine the adrenocortical reserve in patients with chronic tuberculosis during a three days' ACTH test as was done in the group with chronic rheumatoid arthritis, in which the excretion of total 17-OHCS still clearly increased on the second and the third ACTH day (Pekkarinen and Kalliomäki, 1958). In a part of our series of tuberculous patients in the one-day test there may be a low adrenal reserve in the depot ACTH test. In serious cases of tuberculosis it has not been possible to perform an ACTH test lasting several days without antibiotic protection, because the patients have to a great extent been resistant to these agents.

In connection with the operation of lung carcinoma the increase in total 17-hydroxicorticosteroids was very great, especially on the second day after the operation, on the average 34.7 mg; the same was true of the excretions of noradrenaline and adrenaline. From the point of adaptation of the circulation and respiration it is one of the biggest operations, and the maximal reaction of the adrenals and sympathetic nervous system is therefore but natural (Halme, Pekkarinen and Turunen, 1957).

The adrenal function has generally been considered a measure of an individual's ability to resist strain. We know that the Addison patients endure strain very poorly, so that they may succumb already to a small strain, for instance to an infection or an operation without hydrocortisone protection. The resistance of tuberculous patients against noxious factors caused by the disease, for instance continuous fever or endotoxins, is often rather good. This is understandable, because their adrenocortical reserve, judged on the basis of the 17-OHCS excretion, has in most cases been almost normal, which can help the adaptation of the organism to the strain caused by tuberculosis. This good adrenocortical reserve as a result of the adaptation of the organism might be a defence measure in the state of strain due to the chronic tuberculosis. The same observation has been made by Bekaert *et al.* (1957) after the intravenous injection of 20 I.U. of ACTH.

Although the adrenocortical reserve is good during a one day's ACTH test in the majority of the tuberculous patients, in some of the patients the general condition could temporarily be improved by small doses of cortisone during the strain or operation (Cf. Crofton, 1958). The one day's reserve does not show, either, what response the patient's adrenals posses to the strain due to long-lasting tuberculosis. Toxic factors may

then influence the adrenocortical reserve. In tuberculous patients there would be every reason to examine their power of adaptation to the states of strain due to the disease on the basis of the 17-OHCS content in the plasma, and thus make clear the endogenous reaction of the pituitary-adrenocortical system at stress in addition to the ACTH-tests. The necessity of cortisone also depends on the greatness of the strain. The patient may stand small strains well, but during heavy strains some lung tuberculosis patients, also, may need small daily doses of cortisone during short periods. However, overdosage of cortisone during the prolonged period must be avoided.

When it is a question of the excretion of total 17-OHCS in the urine and the evaluation of the adrenocortical function on this basis, it must be taken into account that this excretion is the result of many factors that may have an influence upon its size. It depends on the absorption rate or inactivation of depot ACTH preparation at the place of injection, on the circulation of the adrenals, the formation and secretory capacity of steroids in the adrenals, their metabolism in the tissues, above all in the liver, on the conjugation of these metabolic products with glucuronic acid, and on their excretion into the urine. We must add the biological variation, which has to be taken into account when making conclusions as to the size of the adrenocortical reserve. For practical reasons the determination of the adrenocortical reserve had to be limited to a one-day ACTH test in patients with lung tuberculosis. When evaluating the adrenocortical function as a clinical test we use either a 2 or 3 days' intramuscular depot ACTH test, because experience has shown that in some of the patients the adrenocortical function may not increase clearly until on the second or third ACTH day. In a 5 hours' intravenous ACTH test the increase in the excretion of total 17-OHCS in the urine is observed also during the first ACTH day.

The deficient excretion of total 17-OHCS in 16 per cent of the seriously ill chronic patients in a one day's ACTH test in our series does not necessarily mean that they all had a reduced adrenal function. In a part of these patients a possible adrenal insufficiency might be eliminated in a 2 or 3 days' ACTH test. The adrenocortical reserve has been very good in a part of the patients, and the average reserve during the first ACTH day has been higher than, for instance, that of patients with chronic rheumatoid arthritis and higher than Thorn's average 15 mg level in a one-day ACTH test (Jenkins, Forsham, Laidlaw, Reddy and Thorn, 1955). In the majority of even the most seriously ill chronic tuberculous patients the response of the adrenals to ACTH is normal.

Nevertheless the above mentioned result gives us reason to suppose that steroid treatment would be necessary for some chronic lung tubercu-

losis patients prophylactically during major surgical measures. Seldom, however, operations are carried out on seriously ill patients with pulmonary tuberculosis.

When it is possible to determine the adrenocortical reserve before major operations, the question is of what importance this measure is for a lung tuberculosis patient. The ACTH test can be used as an auxiliary criterion when evaluating the need for prophylactic cortisone treatment before an operation. If a one-day test does not show a sufficiently good adrenal function reserve, we recommend rather to use a two or three days' depot ACTH test (80 units/day) or alternatively a one-day intravenous ACTH test with 25 units, together with antibiotic therapy. In tuberculosis sanatoriums these tests can be performed in good time before the operation and the adrenals get sufficient time to recover. An ACTH test before operation has been considered beneficial for the adrenal function during the operation (ch. Hartenbach, 1957). The prophylactic beginning of hydrocortisone treatment may be preferred before major operations in seriously ill patients. In adrenal insufficiency treatment, prophylaxis with hydrocortisone is always more favourable than therapy, if needed, after operation.

SUMMARY

The adrenocortical excretion was studied in 104 seriously ill tuberculous patients in a one-day ACTH test (80 units Cortrophin Z depot i.m.). The patients were at the severe and chronic stage of the disease: 35 patients belonged to stage II and 69 to stage III (according to Forsman's and Larmola's classification). In 9 patients the same test was repeated. Of the patients 69 were men and 35 women. Their average age was 40.6 years.

The average basal excretion of total 17-OHCS was 3.8 mg/day (men 3.5 and women 4.2 mg). During the ACTH day the average excretion was good, 21.5 mg (men 20.9 and women 22.7 mg). There was an excretion above 30 mg in 22 patients, above 21.5 mg in 54 patients, and above 10 mg in 87 patients. 17 patients had an excretion of less than 10 mg. The excretion was good in old patients (above 50 years). It was higher in thin (0.38 mg/kg/day) than in obese patients (0.29 mg/kg/day), but the total excretion was nearly similar in both groups of thin and normal weight. The adrenocortical excretion during the ACTH day had no correlation to the stage of the disease nor to clinical findings, as for instance fever or complications.

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FROM THE DEPARTMENT OF MEDICAL MICROBIOLOGY,
UNIVERSITY OF TURKU

THE REDUCTION OF NITRATE BY MYCOBACTERIA

By

SIMO VIRTANEN

The typing of mycobacteria has been based primarily on the results of animal experiments. The pathogenity of the bacteria to animals has permitted division into the following major types: human, bovine, avian, and the heterogeneous group of acid-fast saprophytes. As, however, the virulence to guinea-pigs of bacteria resistant to INH is very low or almost nonexistent, it is often very difficult to distinguish these species from saprophytes and BCG strains. This problem existed even before INH was introduced, for strains had been isolated from lupus cases whose pathogenity to guinea pigs had been weak and whose identification had met difficulties (2).

Besides the usual animal tests, it is possible to use for differentiation mice tests, the intracutaneous guinea-pig test, growth in cultures at different temperatures and in different nutrient media, drug resistance determinations, catalase activity measurements, penicillinase formation, and chemical tests such as the methylene blue, neutral red, cyanogen bromide and arylsulphatase tests. Of these it may be said that none is reliable alone, but a more accurate differentiation is generally possible when several tests are carried out concurrently. In the following, another test — a nitrate reduction test — is described, which shows promise of being of value in the differential diagnosis of the mycobacteria.

The tests are carried out using a 0.01 molar sodium nitrate solution, either in a phosphate buffer solution or in Dubos' liquid medium. A preliminary qualitative test is usually performed by inoculating the buffer solution with one loopful of bacteria. In the quantitative tests 10 milligrams of bacterial mass from a solid nutrient medium is weighed and the tests are carried out at least in duplicate.

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The formation of nitrite can be detected by adding sulphonamide and N-(1-naphthyl)ethylenediamine-dihydrochloride to the test solution acidified with hydrochloric acid (4). The intensity of the deep violet colour that develops is measured with a photometer.

The qualitative tests of nitrate formation were performed in a phosphate buffer of pH 7.0. The cultures on Finlayson egg medium (1) from which the bacterial specimens were taken were of the following ages: human, 4 weeks; bovine, 4—6 weeks; avian, 2 weeks; and saprophytes, 2 weeks.

The intensity of the colour produced has been graded as follows: + very weak colour just deviating from the control, ++ violet colour of medium intensity, +++ very intense violet colour.

The results of some qualitative tests are shown in Table 1. The bovine

TABLE 1

Nitrate-reducing activities of 822 mycobacteria

Species	Number Showing Nitrate Reductase Activity of Degree				No. of Strains Examined
	+++	++	+	–	
M.tuberculosis					
Human type	742		1	7	750
Bovine type			2	21	23
Avian type	5			7	12
BCG			1	4	5
Acid-fast saprophyte ..	8	4	2	9	23
H 37 Ra	1				1
R_1Ra	1				1
R_1Rv	1				1
M.balnei				1	1
M.muris				1	1
M.phlei	1				1
M.piscium				1	1
M.ranae	1				1
M.smegmatis	1				1

as well as the BCG strains were either negative or very weakly positive. The reactions obtained with the avian and acid-fast saprophytic strains varied from strongly positive to negative. International avirulent strains H 37 Ra, R_1Ra and a low-virulent R_1Rv strain all gave positive reactions. Of 750 human strains, 742 gave strong positive reactions, one a weak positive and seven negative reactions. The latter eight strains could not be distinguished by the growth properties from ordinary human or BCG strains. In the ordinary guinea-pig tests they were of low-virulence and

gave rise to only a weak local inflammatory process in the inguinal nodes. In the intracutaneous guinea-pig tests (3) the strains were as virulent as or less virulent than the BCG strain from the Danish Serum Institute that was employed as the control strain.

The results of drug resistance tests, the origins of the specimens and the clinical diagnoses of the patients are given in Table 2. Five of the

TABLE 2

Origins and drug sensitivities of seven strains giving negative nitrate-reduction tests and of one strain giving a weak positive test

Strain No.	Specimen	Clinical Diagnosis	Sensitivity Test		
			INH	PAS	SM
206	Sputum	Tub. pulm.	s	s	s
246	Pus	Osteomyelitis	s	s	s
278	Sputum	Tub. pulm.	r	s	s
286	Sputum	Tub. pulm.	r	s	s
444	Sputum	Tub. pulm.	s	s	s
456	Sputum	Tub. pulm.	s	s	s
492	Sputum	Tub. pulm.	s	s	s
S9/57	Pus	Lymphadenitis ing.	90 % s 10 % r	s	s

s = sensitive
r = resistant

strains were sensitive to all common antituberculotic drugs. One was completely resistant to INH and grew on Finlayson's egg medium containing 50 mcg of INH. Two strains contained INH-resistant variants, which also grew in the tube containing 50 mcg of INH. The strains 246 and S9/57 had been isolated from a patient who had received the BCG vaccination.

Typical curves obtained in the quantitative tests are shown in Fig. 1. The tests were carried out with 10 mg of bacterial mass in nitrate-containing phosphate buffer solution of pH 7.0. Typical human and positively reacting saprophyte strains gave similar curves as the H 37Rv and *M.phlei* strains. The bovine and BCG strains were either negative or yielded lower values than *M.bovis* 622 and the Behring-Werke BCG strains.

Nitrate is evidently reduced only to nitrite by mycobacteria. The strains were not observed to reduce nitrite.

The rate of nitrate reduction by positive strains remains constant

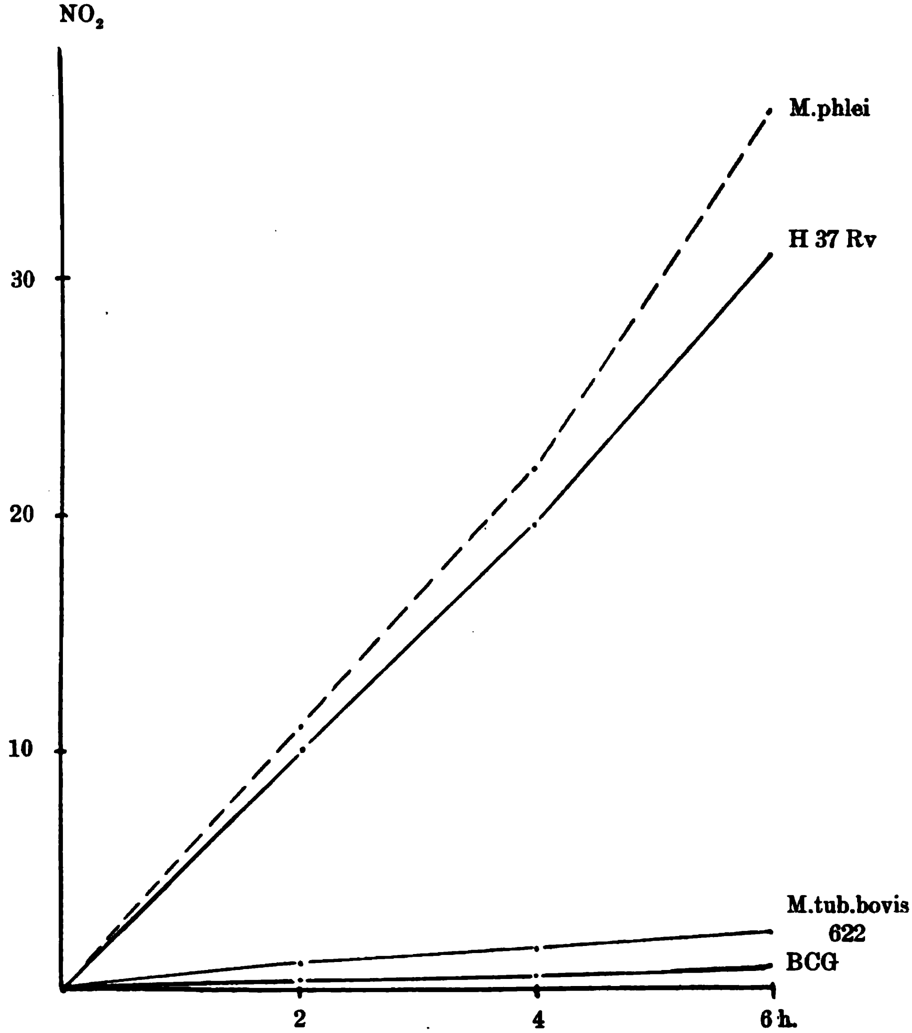

Fig. 1.

Results of quantitative tests with several type strains
Abscissa: Time of incubation. Ordinate: Drum readings of photometer showing amount of nitrite formed.

and strains that gave negative tests could not be adapted by employing either the buffer solution or Dubos' liquid medium. The ability to reduce nitrate diminishes with the age of the culture.

Heating to 100° C destroys the reducing properties of the strains. Toluol added to the bacterial mass resulted in a negative test. The result is not influenced by performing the test in air, hydrogen or a vacuum.

The effect of enzyme inhibitors is shown in Table 3.

TABLE 3

Effect of some enzyme inhibitors on nitrate reduction by mycobacteria

Inhibitor		Per Cent Inhibition after 2	4	6	24 h.
Sodium iodoacetate	0.01 M	74	81	86	87
NaN_3	0.01 M	49	68	74	73
NaF	0.01 M	49	67	69	48
Sodium malonate	0.01 M	42	51	54	40
KCN	0.01 M	100	100	100	97

No correlation was established between the nitrate reduction and tetrazolium reduction tests. Slightly lower values were obtained in the latter test for the BCG and bovine strains than for the human strains. *M.avium* and the saprophytic strains usually gave fairly high values irrespective of their ability to reduce nitrate.

The writer is of the opinion that the nitrate reduction test is of value in the differential diagnosis of tubercle bacilli, primarily in distinguishing bovine and BCG types, strains resembling BCG types and, in some degree, saprophytic mycobacteria from human species.

SUMMARY

The author has examined the nitrate-reducing ability of mycobacteria in phosphate buffer solution. Of 750 *M.tuberculosis* strains of human type, 742 gave a strong positive colour reaction, 7 no reaction and one strain a very weak positive reaction. The latter 8 strains were found to be attenuated in guinea-pig tests and effected only local reactions at the site of injection. Five BCG strains from different sources gave a weak positive result in one case and a negative result in 4 cases. Two of 23 strains of bovine type gave weakly positive tests and the remainder negative tests. Twelve of 23 acid-fast saprophytes gave strong positive reactions, two weakly positive reactions, and 9 negative reactions. Mycobacteria reduced nitrate only to nitrite. The test is considered to be of value in the identification of mycobacteria.

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A PECULIAR TUBERCULOSIS DISTRICT IN THE ARCHIPELAGO OF ÅBOLAND

By

INGA SCHRÖDER [1]

A short account of the anti-TB campaign by m/s "Gullkronan"; its development since 1951; stressing the day to day work; limited statistical information; colour slides.

[1] The Tuberculosis District of Raseborg, Turku, Finland.

FROM SATAKUNTA SANATORIUM, HARJAVALTA, FINLAND

DIAGNOSIS OF PULMONARY TUMOURS IN SANATORIA

By

RISTO ELO

This paper is based on our experiences in the diagnosis of tumours of the lung in the Satakunta Sanatorium in 1955—57.

During this period a total of 35 cases of bronchial carcinoma were diagnosed in the sanatorium. The distribution of the cases by age and sex is shown in table 1.

TABLE 1

Cases of bronchial carcinoma in 1955—57

Age, Yrs.	35—39	40—44	45—49	50—54	55—59	60—64	65—69	70—74	Total
Male	2	1	1	(2) 8	(3) 10	3	(1) 3	(1) 1	29
Female	0	(2) 2	0	0	2	0	(1) 2	0	6
Total	2	3	1	8	12	3	5	1	35

In addition to the clinical examination, the following criteria were applied in the diagnosis of the cases stated in parentheses: Sputum contained definite tumour cells (6), pleural puncture yielded definite tumour cells (2), diagnosis by explorative thoracotomy (1), metastases from carcinoma of the prostate (1), total 10 cases. In the remaining cases (25), bronchological examinations were decisive in establishing the diagnosis. A study of the rôle of the latter examination is of interest.

In 1955—57 a total of 758 bronchoscopic examinations were made in this sanatorium, and in 86 cases (11.3 per cent) the indication was a suspected tumour. These patients were distributed by age and sex as follows:

TABLE 2

Patients with suspected tumour

Age, Yrs.	35—39	40—44	45—49	50—54	55—59	60—64	65—69	Total
Male	5	8	15	21	18	8	3	78
Female	3	0	1	0	2	0	2	8
Total	8	8	16	21	20	8	5	86

A bronchial carcinoma was diagnosed in 25 (29 per cent) of these patients. The distribution of the findings is seen in table 3, in which also are included the results of thoracotomies, pleural punctures and scalenus biopsies.

TABLE 3

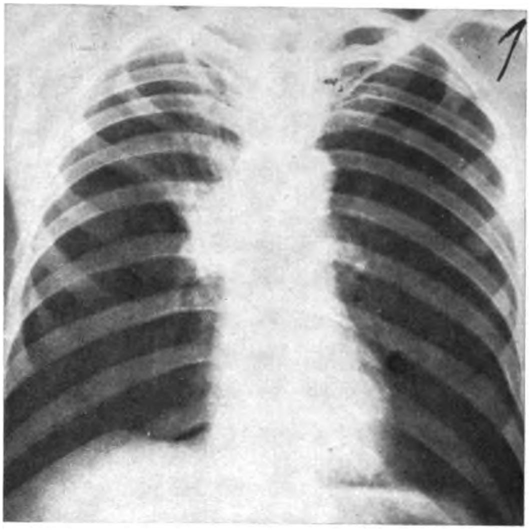
Bronchoscopic findings in patients with tumour

	Tumour Cells +	Tumour Cells —	Tumour Cells Suspected
Sputum	8	15	2
Aspiration	6	4	1
Biopsy	16	0	2
	30	19	5
Thoracotomy	4	0	0
Pleural puncture	3	1	0
Scalenus biopsy	0	1	0
Total	37	21	5

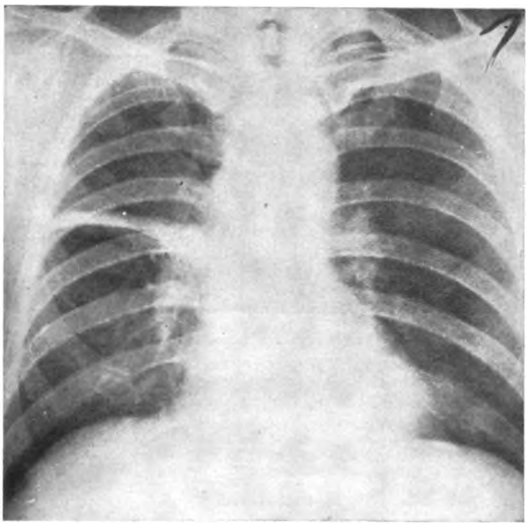
As is seen, there were 26 negative or doubtful cases, which were confirmed by a total of 37 positive findings, since two kinds of positive evidence was obtained in many cases.

The bronchoscopic and other findings in the 61 cases in which a diagnosis of tumour was not made are shown in table 4.

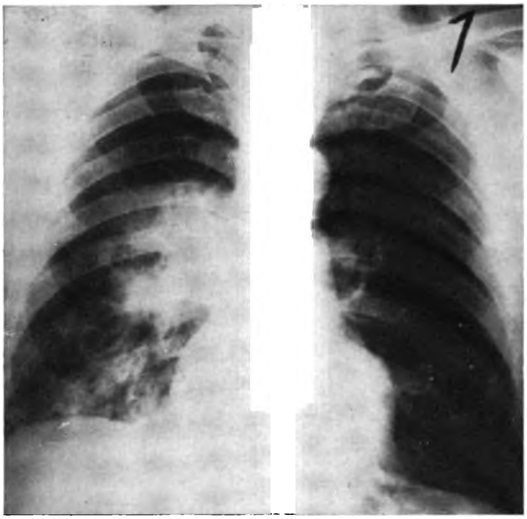
Suspected tumour cells were found in 11 patients but on re-examination the finding was a negative one. The total number of findings was 107, since several results were obtained in many cases. Table 5 shows the final diagnosis in the non-tumour cases.



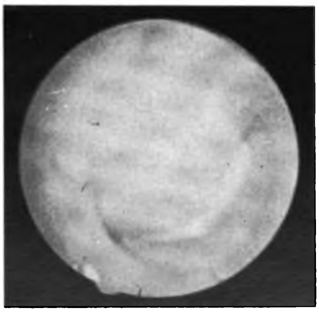
Case 1.

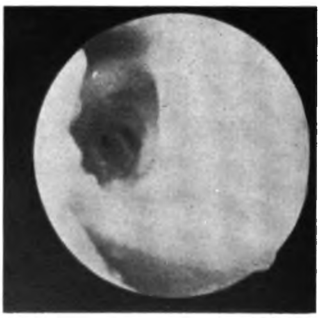


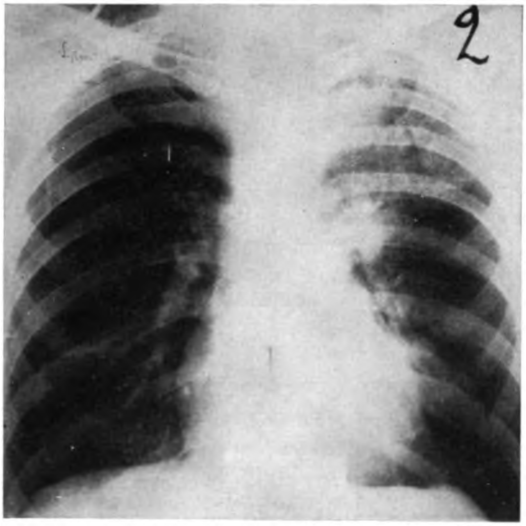
Case 2.

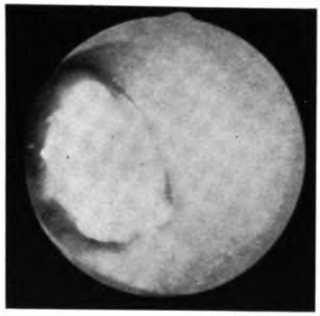


Case 3.

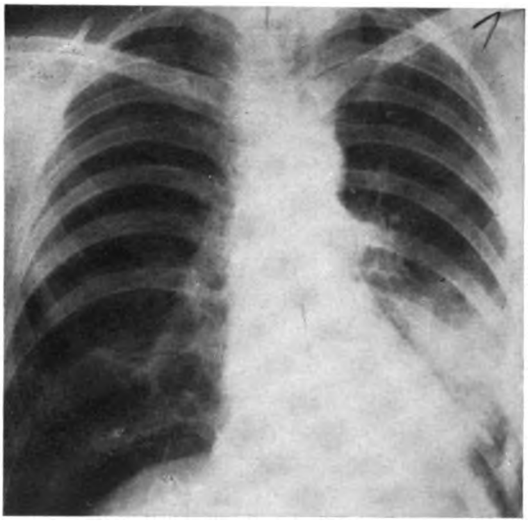


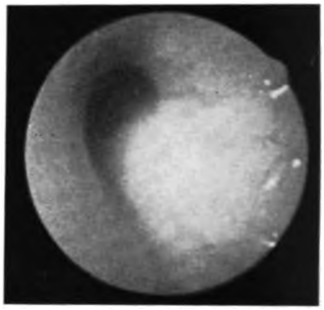






Case 4.





Case 5.

TABLE 4

Bronchoscopic findings in non-tumour patients

	Tumour Cells —	Tumour Cells Suspected
Sputum	45	6
Aspiration	36	3
Biopsy	8	2
	89	11
Pleural puncture	4	0
Thoracotomy	2	0
Scalenus biopsy	1	0
Total	96	11

TABLE 5

Final diagnosis in non-tumour cases

Bronchitis chron. (et emphysema pulm.)	13	St.post adscessu pulm.chron.	2
Pleuritis chron. seu cicatricas seu resid. post pleuritim	12	Anomalia bronchi	1
Resid. p. pneumoniam	11	Tumor benignum	1
Tub. pulm. seu tuberculoma (2)	11	Myeloma multiples	1
Bronchiectasiae	3	Tub. bronchialis	1
Haemoptysis et atelectasis	3	Asthma bronchiale	1
		Empyema chron. pleurae	1

The great majority of these diagnoses comprised chronic bronchitis and the early or after states of pleuritis and pneumonia. This fact is significant, especially since the mean age of sanatorium patients is increasing. The high incidence of tuberculosis (11 cases) presumably points to the difficulties encountered in its diagnosis. There were two patients in this series with coexistent tuberculosis and bronchial carcinoma; these cases are included in the figure for carcinoma.

We have also paid special attention to involvement of the bronchi by carcinoma with a view to treatment. Bronchographs of the tumour region are taken in connection with bronchoscopy, to serve as a valuable aid to the clinician and the surgeon in considering the indications and prognosis of surgical treatment.

I shall briefly describe five cases in my series.

Case 1. — N. R., hosp. rep. No. 25087, was a farmer aged 50. Since autumn 1956 there had been cough; haemoptysis had occurred in February 1957. He was treated at the sanatorium during which time the findings

were: tbc micr. 10 x : —, tbc cult. 6 x : —, tumour cells in sputum: —. Bronchoscopy revealed a large tumour filling the lower portion of the trachea and the posterolateral portion of the right main bronchus. PAD: *Carcinoma epidermale bronchi.* 3 diapositives. The patient was transferred to irradiation treatment.

Case 2. — K. K., hosp. rep. No. 25207, a 44-year-old carpenter, in whom exudative pleuritis on the right had been diagnosed in November 1956. In March 1957 there was fever and stitch, and an interlobular pleuritis or atelectasis was seen in the right lung. He was in the sanatorium, where tbc micr. 10 x : — and tbc cult. 9 x : —. Examinations for tumour cells were not made. Bronchoscopy: The lower portion of the trachea, the carina and the right main bronchus were infiltrated by a tumour. PAD: *Carcinoma epidermale bronchi.* 4 diapositives. Patient was transferred to irradiation treatment.

Case 3. — E. P., hosp. rep. No. 25281, a farmer aged 54, had had bouts of fever and dyspnoea in April and May 1957. He was treated at the sanatorium, when the following findings were made: tbc micr. 7 x : —, tbc cult. 5 x : —, tumour cells: +. Bronchoscopy: Above the bifurcation of the middle lobe bronchi the main bronchus was almost completely occluded by a tumour arising from its lateral portion. PAD: *Carcinoma epidermale keratinosum bronchi.* 3 diapositives. The patient was transferred to irradiation treatment.

Case 4. — A. L., hosp. rep. No. 25139, a building contractor aged 52, had had occasional fever in March 1957 and changes had been seen in the left lung. At the sanatorium the finding were: tbc micr. 5 x : —, culture 12 x : —. Tuberculosis was suspected at first and he was given *ex juvantibus* antituberculosis medication, resulting in recession of the roentgenological changes (simulated cure). Tbc cultures continued to be negative and the patient complained of dyspnoea in all positions. Bronchoscopy showed a normal main bronchus on the left and a nodular, partly necrotic tumour arising from the lateral wall of the upper lobe bronchus. PAD: *Carcinoma spinocellulare bronchi.* 3 diapositives. Surgical treatment: *Pulmonectomia sin.* About 10 months after the operation the patient is well and working halfdays.

Case 5. — E. S., hosp. rep. No. 25443, a 53-year-old labourer, complained of constant "smoker's cough". Following influenza in October 1957 he was tired and lost weight. He underwent treatment at the sanatorium, tbc micr. 6 x : — and tbc cult. 6 x : —. Bronchoscopy: Complete infiltration of the carina by tumour tissue and narrowing of both main bronchi. PAD: *Carcinoma microcellulare pulmonis.* 3 diapositives. The patient was transferred to irradiation therapy.

To summarize, it may be said that the diagnosing of tumours of the lung is an important part of the work in a sanatorium. Although the diagnosis of some of the cases is possible clinically, bronchological examination plays an important rôle in this work. Bronchoscopy facilitates an accurate consideration of the indications for operation.

In the differential diagnosis, bronchitis and conditions following pneumonia and pleuritis appear to cause some difficulty, especially in the older age groups. Care should be taken not to be misled by apparent cures seemingly obtained with medical therapy for pneumonia.

DISCUSSION

Alf Westergren, Sweden:

With reference to this paper on the diagnosis of pulmonary tumors in a sanatorium series, I feel bound to point out that concomitant lung carcinoma and tuberculosis do not seem to be so very rare; and there is fairly often reason to surmize that cancer commences to develop in an area of tuberculous lesions, usually healed. In Nordisk Medicin, 1957 (volume 58, page 1971) I communicated a survey comprising 100 cases of primary carcinoma of the lung, 33 of which had evidently begun in that way and a further 22 may have done so. I have since learned that some similar surveys had been reported earlier and later, including a major one from Switzerland in which the incidence of such associations of cancer and tuberculosis was almost the same as in my series (to be published more fully in Acta Chirurg. Scand. in 1959).

ENDOSCOPIC ASPECT OF BRONCHIAL CHANGES IN PULMONARY TUBERCULOSIS

By

Tauno Palva

(Is published in Acta Tuberculosea Scandinavica 1958:38:120)

FROM THE DEPARTMENT OF PATHOLOGICAL ANATOMY, SECTION II, (CHIEF: PROF. H. TEIR), AND FROM THE DEPARTMENT OF SEROLOGY AND BACTERIOLOGY (CHIEF: PROF. K. O. RENKONEN), UNIVERSITY OF HELSINKI

MICROBIOLOGIC AND HISTOLOGIC OBSERVATIONS ON SPECIMENS FROM RESECTED TUBERCULOUS LUNGS

By

KARI ASP

In considering the indications for resection of the lung and especially in determining the extent of the resection required, it is important to know what effect medical treatment will have on the disease process. A clinical examination and a resistance test of the bacteria in the sputum will give some information in this respect. To obtain an idea of the effect of chemotherapy on the tissue, I have compared the microbiologic investigation results and the histologic features of tissue specimens.

MATERIAL AND METHODS

The series consisted of 75 patients with pulmonary tuberculosis treated by resection in 1957—1958. For microbiologic and histologic examinations a sample was taken of each patient from, if possible, the main focus, usually from the wall of the cavity, and from the bronchus leading to the focus, from another focus in the lung, and from the hilar lymph nodes. Histologic preparations were made from all the specimens using haemalum-eosin and van Gieson's staining methods. Eskelund's Nile blue-saffron staining was used for the demonstration of tubercle bacilli in the tissues. Tubercle bacillus and fungus cultures were prepared from the main focus, the additional focus and the hilar nodes. For this culture the tissue was pulverised in a mortar with physiological saline to form an even suspension, from which the fungus cultures were made on Sabouroud, oil Sabouroud and thioglyconate culture media. After treatment with 1 per cent hydrochloric acid for 12 hours, tbc cultures were

made into test tubes containing Löwenstein—Jensen culture medium. The fungus cultures were read 10 days and the tbc cultures 6 weeks after inoculation. The microbiologic examination was made of all patients in the series, and the histologic examination has been carried out to date on 25 patients [1].

RESULTS OF EXAMINATIONS

Results of Tubercle Bacillus Cultures

The tubercle bacillus cultures made from the resected specimens were, on the average, positive in 31 per cent of the specimens. The results of the cultures grouped according to the site from which the specimen was taken are shown in Table 1.

TABLE 1

Results of Tubercle Bacillus Cultures

Origin of Specimen	Positive	Negative	Total
Main focus	36	39	75
Other focus	18	57	75
Hilar lymph node	15	60	75
Total	69	156	225

Stainings for tubercle bacilli were also made of the histologic specimens from 25 patients. All the specimens in which the culture was positive showed bacilli also in the histologic specimen. In addition, bacilli were found in 79 per cent of the histologic specimens which gave a negative tbc culture.

Before operation all the patients in the series had been given specific chemotherapy, using combined SM-PAS-INH treatment. Since the medical treatment was similar in all the cases, the patients are grouped only according to duration of the treatment. Table 2 shows the effect of the chemotherapy on the results of the cultures. The positive cultures are stated in the table as percentages of the total. The percentages of positive preoperative sputum stainings are also stated for comparison.

[1] The results for the entire series of patients will be published later.

TABLE 2

Effect of Duration of Antibiotic Therapy on Sputum Stainings and Tissue Cultures

Duration of Chemotherapy	Sputum Stainings Positive for Tbc %	Culture of Specimens Positive for Tbc		
		Main Focus %	Other Focus %	Hilar Lymph Nodes %
0— 6 months	44	48	17	10
7—12 „	37	44	22	15
Over 12 „	63	48	37	37

Results of Fungus Cultures

The results of the fungus cultures from the tissue specimens, grouped according to origin of the specimen, are shown in Table 3.

TABLE 3

Results of Fungus Cultures

Origin of Specimen	Positive	Negative	Total
Main focus	14	61	75
Other focus	14	61	75
Hilar lymph nodes	10	65	75
Total	38	187	225

Of the specimens, 29 yielded fungi of Penicillium species and 9 yielded Candida. Penicillium was encountered evenly in various foci, while Candida favoured the walls of cavities. The positive fungus cultures were evenly divided between the specimens from which the tubercle bacillus culture was positive or negative.

Histologic Findings

A histologic examination was made of a total of 125 tissue specimens from 25 patients. Attention was paid especially to the features that may be regarded as typical of the effect of chemotherapy. Based on the earlier investigations of, among other workers, Canetti, Denst, Auerbach, and Turunen *et al.*, the criteria of a favourable chemotherapeutic effect may be considered to consist of a few typical changes, such as absence of recent pneumonia, decreased perifocal inflammation, frequently manifesting as necrosis bordering on the connective tissue without a zone of granulation

tissue rich in inflammatory cells (Fig. 1), a small number of tubercles, and an abundance of giant cells resempling foreign body giant cells (Fig. 3). The evaluation of the effect of the chemotherapy on the disease process was based on the general histologic picture and the above mentioned criteria.

Table 4 shows the histologically evaluated effect of the chemotherapy in correlation to the duration of the therapy and to the combined results of the tbc cultures.

TABLE 4

Comparison of Histological Effect of Chemotherapy, Duration of Chemotherapy, and Cultures for Tbc

Effect of Chemotherapy	No. of Patients	Duration of Chemotherapy		Results of Tissue Cultures for Tbc	
		0—6 Months	Over 6 Months	+	—
Favourable	10	4	6	2	28
Poor or absent	12	7	5	18	18
Indefinite	3	1	2	—	3
Total	25	12	13	20	55

In three cases the changes were so slight that no histologic evaluation could be made.

DISCUSSION

Tubercle bacillus cultures made from specimens from resected lung portions were about twice as frequently positive in the main focus as in other sites. This is in agreement with the results reported by Bloch *et al.* Attention is especially drawn to the small number of positive findings in the cultures from the hilar lymph nodes. In the corresponding examinations by Pätiälä *et al.* and Turunen *et al.*, the number of positive cultures was considerably greater.

In observing the effect of medical treatment on the results of the cultures for tubercle bacilli it may be observed that in the cases in which the duration of the treatment was longest, bacilli were obtained somewhat more frequently from the minor focus and the hilar lymph node. This is in part ascribable to the fact that in the patients who had received treatment for a longer time the disease process was of greater severity and of longer duration.

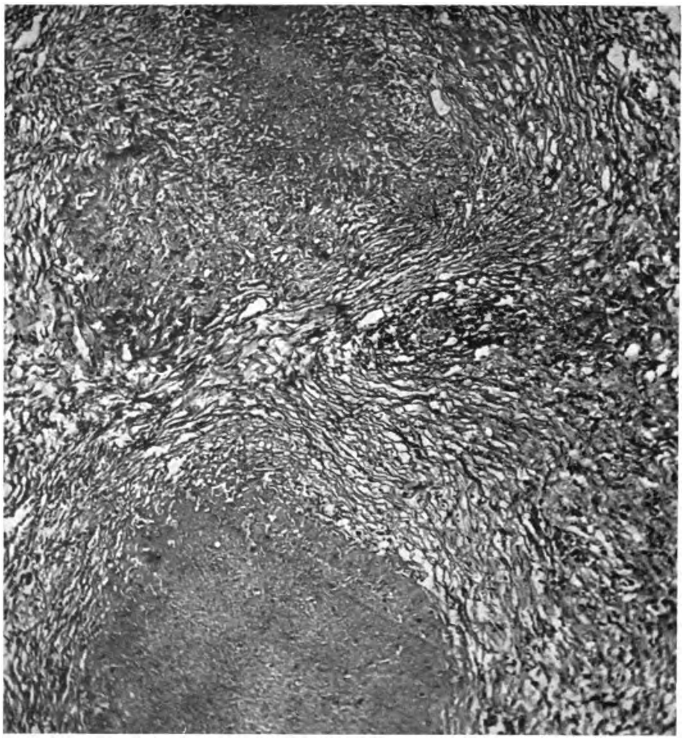


Fig. 1.

Necrosis is in contact with the connective tissue without a zone of granulation tissue. × 100.

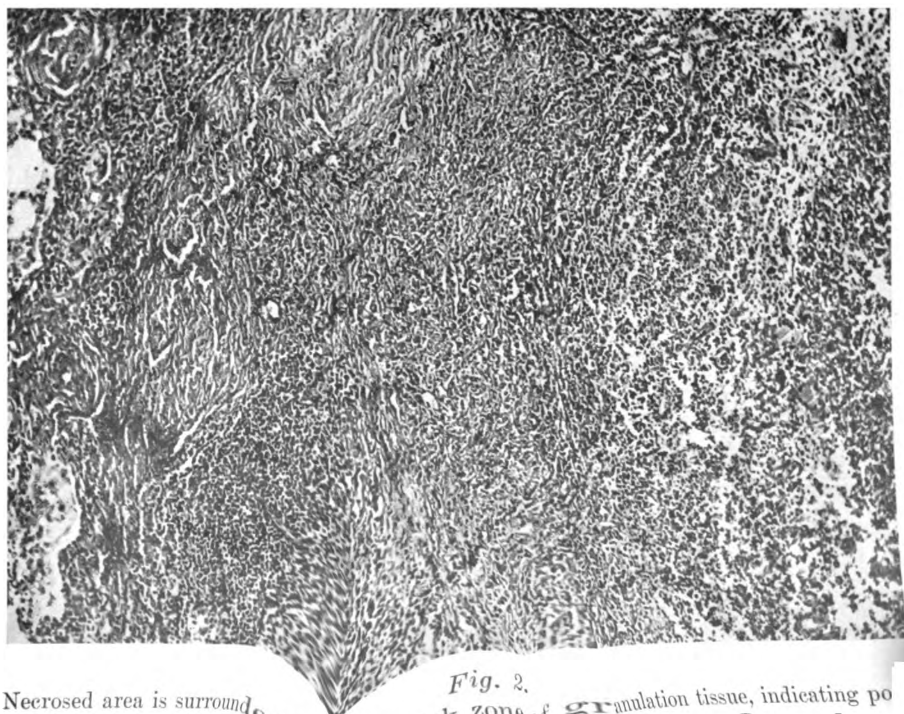


Fig. 2.

Necrosed area is surrounded a thick zone of granulation tissue, indicating po peutic effect. × 100.

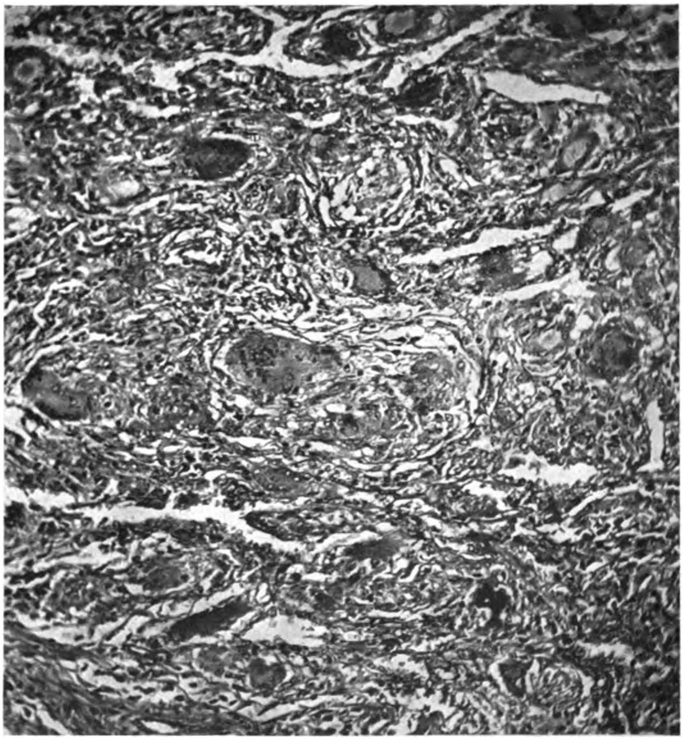


Fig. 3.
Photomicropraph showing several polymorphic giant cells. × 200.

Bacilli were found in the stained histologic specimen in 79 per cent of those specimens which gave a negative culture. This may be a result of a deficient culture technique or, according to Dubos, of the tuberculosis bacillus being brought by the antibiotic to a condition where it cannot multiply in the culture medium.

Regardless of the chronic nature of the disease and of the freguently long duration of the chemotherapy, relatively few fungi were found, a positive culture being obtained in 17 per cent only. A comparison of the results of fungus cultures and the duration of the chemotherapy reveals no marked differences between the groups of patients receiving antibiotic treatment for different lengths of time. A finding worthy of special note was the occurrence of fungi of species Candida in the wall of a cavity containing a large number of tubercle bacilli. In the investigation by Mankiewicz, tubercle bacilli promoted the growth of Candida *in vitro*.

In the histologic examination a favourable antibiotic effect was seen in less than half of the patients. The favourable result was not found to be correlated to the duration of chemotherapy. The histologic examination seemed to indicate that it would be a valuable adjunt, beside other criteria, in evaluating the effect of chemotherapy and the nature of the disease process. Frozen slices made and examined during the resection operation may provide indications concerning the necessary extent of the resection, especially in cases in which all the observed foci cannot be removed. In addition, it gives hints in the planning of postoperative treatment.

SUMMARY

The author carried out cultures of tubercle bacilli and fungi as well as histologic examinations of specimens from resected lungs of 75 patients with pulmonary tuberculosis treated by chemotherapy. The tbc cultures were positive in an average of 31 per cent of the specimens. A positive result was obtained about twice as frequently from the main focus as from specimens taken from other portions of the lung. The duration of chemotherapy was not found to be related to the result of the cultures.

Cultures for fungi were positive in an average of 17 per cent of the specimens. Fungi of the species Penicillium and Candida occurred most commonly.

In the histologic examination the object was to determine the effect of the chemotherapy on the tissues. A favourable effect was observed in less than half of the patients. Frozen slices removed and examined during operation may serve to give indications concerning the extensiveness of the resection and the postoperative chemotherapy.

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DISCUSSION

J. Lehmann, Sweden:

According to investigations from dr. Dubois laboratory at the Rockefeller Institute in New York, saline is toxic to the tubercle bacillus. Better results are obtained when the tissue is suspended in 0.1 per cent bovine albumin. Have you tried this?

Kari Asp:

In another connection I used as parallel suspension media Tween-albumin and physiological saline. The cultures in the two cases gave corresponding results.

A STUDY OF THE DISTRIBUTION OF LABELLED PAS IN THE HUMAN BODY

By

ÅKE HANNGREN

Tritium, the mass three isotope of hydrogen (triple weight hydrogen) was used in this study as the tracer. A sufficiently high specific activity was obtained to permit autoradiographic examination of the distribution of the medical substance in the body. Intracellular localisation of PAS was demonstrated in cartilage and connective tissue. Furthermore it was possible to demonstrate localisation to the adrenals, thyroid and salivary glands. PAS also accumulated in tuberculously changed tissue of a proliferative nature. Experimentally induced lung cavities in guinea pigs and lung cavities in resected specimens from human patients showed poor diffusion of PAS into the cavity contents but a high concentration in the cavity walls. (Editor's abstract.)

FROM THE CENTRAL LABORATORY, MUNICIPAL HOSPITAL, AALBORG, AND THE SKØRPING SANATORIUM, DENMARK.

PROBLEMS IN PAS DOSAGE

By

H. O. BANG and E. STRANDGAARD

The overall results of this study combined with two previous investigations, of which it forms a continuation, were as follows:

The PAS concentration in the blood was studied by the Lehmann method in about 2,500 blood samples from about 160 patients during treatment with various PAS compounds.

The blood level is a valuable aid in controlling the efficacy of the treatment, in selecting the most suitable preparation, and in fixing the dosage.

Aminosalyl calcium, in the form of PAS-IDO calcium granulate, in doses of 6 g twice daily or 3 g three to five times daily, gives a PAS concentration in the blood of from 3—4 mg per 100 ml up to 12—14 mg per 100 ml, maintained throughout the day. This compound was tolerated by threequarters of the patients with no side effects or with only negligible dyspeptic complaints.

Aminosalyl sodium, in the form of PAS-IDO sodium granulate, in an aqueous solution of powders made at the hospital dispensary and dissolved immediately before use, or in the form of tablets made by Wander and administered in does of 3—4 g three to four times daily, gave blood levels ranging from 2—4 mg per 100 ml up to 8—10 mg per 100 ml.

The use of phenyl PAS, in the form of Tebamine Leo tablets, powders, or emulsion, administered in doses of 3—5 g three times daily, gave somewhat capricious results. In most instances the concentrations were low, about 1—3 mg per 100 ml, while in other cases there might be capricious fluctuations up to 5—6 mg per 100 ml, and only in rare cases a constant increase up to 7—8 mg per 100 ml in the evening.

PAS THERAPY WITH A DAILY UNFRACTIONATED DOSE

By

NILS RISKA

(Will be published in the Acta Tuberculosea Scandinavica)

FROM THE HELSINKI TUBERCULOSIS HOSPITAL,
CHIEF: K. KIVIKANERVO, M.D., DOC.

A FOLLOW-UP STUDY OF PATIENTS WITH PULMONARY TUBERCULOSIS TREATED WITH COMBINED CHEMOTHERAPY[1]

By

K. KIVIKANERVO, MAIJA WÄRE-NISKANEN and H. POPPIUS

The part of the examinations that is the object of this report consists of 110 survivors among conservatively treated tuberculous patients with one or more cavities which closed in 3—12 months of combined drug treatment. The initial extent of the disease is shown in Table I. All were bacteriologically tb-positive before treatment and the organisms were estimated as sensitive to the three standard drugs. None of the patients had been previously treated with antituberculotic drugs.

TABLE 1

Relapses among 110 survivors treated with chemotherapy alone related to initial extent of disease and duration of chemotherapy.

Duration of Chemotherapy in Months	Extent of Disease					
	Far Advanced		Moderately Advanced		All Cases	
	No.	Relapses	No.	Relapses	No.	Relapses
6— 8	10	5	16	5	26	10
9—11	12	1	7	2	19	3
12—17	8	1	8	0	16	1
18—23	22	0	14	0	36	0
24+	9	0	4	0	13	0
Total	61	7	49	7	110	14

Results: All 110 patients were tb-negative in cultures made, at the latest, after six months of treatment.

[1] This short preliminary report concerning the frequency of relapses in patients with pulmonary tuberculosis is part of a larger follow-up study which will be published later.

The number of relapses was studied during the observation period of 22—54 months after cavity closure. In Table I is shown the number of observed relapses. As relapse was considered the evidence of resumed activity of the disease after tb conversion and cavity closure had been achieved. Such evidence consisted of radiological deterioration and or reversion to positive bacteriology. There were 13 relapses during the first 2 years after cavity closure in patients who had received chemotherapy for less than 1 year. The only relapse in the group given chemotherapeutic drugs during 1—1 ½ years had actually received drug treatment for only 12 ½ months and belonged to the group of far advanced cases. There were no relapses in patients treated for 1 ½ years and more.

It is possible that some more relapses may occur later on, but this study shows that the duration of chemotherapy is a very important factor in determining the rate of early relapses.

SENSITIVITY REACTIONS DURING ANTIBACTERIAL TREATMENT OF TUBERCULOSIS

By

SVEN STAVENOW

The author described an investigation of allergic manifestations in a pulmonary tuberculosis series treated by chemotherapy at the Lung Clinic of St. Göran's Hospital, Stockholm. Attempts were made to analyse more closely the circumstances connected with the onset of the reactions, especially the condition of the products administered. The changes in the blood picture associated with the allergic reaction were studied by means of repeated provocation tests.

DISCUSSION

J. Lehmann, Sweden:

I thank you for the interesting papers on PAS. Especially I find Dr. Hanngrens investigations of interest. I think that this kind of basic investigations will contribute substantially to our understanding of the effectivity of PAS in the different organs and perhaps can serve as a guide for finding the most adequate regimen for the treatment. In the following I will present the result of some experiments indicating that PAS preferably should be given in a few large doses instead of many small doses. I have studied the fate of PAS on its way through the body (guinea-pig and human) from its passage through the intestinal mucosa and the different organs until it is excreted in the urine. PAS is conjugated with acetyl- and glycyl-groups, respectively, into inactive products in all tissues except muscle tissue. The highest conjugation capacity is located in the liver, kidney and instestinal mucosa. If very small doses of PAS are given, all of it will become conjugated and no free bacteriostatic PAS will appear in the blood. If the doses are increased, the conjugating capacity of the body is exceeded and free PAS is found in the blood and urine but the main part is still inactivated by conjugation. At still higher doses, more free PAS is found and if the concentration in the blood exceeds 10 mg % a new phenomenon will be observed: the acetyl-conjugating enzyme is poisoned assumingly by the free PAS, resulting in an addition of approximately 20 % to the concentration of free PAS — both *in vitro* and *in vivo*. With these findings in mind it is easy to understand why very low concentrations of free PAS are found when slowly absorbed preparations, such as benzoyl-PAS and similar compounds, are taken: The slow appearance of PAS in the blood will allow the conjugating capacity of the cells to conjugate and inactivate the main part of PAS. It is my opinion that we should abandon all these preparations which are slowly absorbed or which slowly liberate PAS, as they are uneconomic due to the inactivation of PAS and often ineffective due to too small concentrations in the blood and tissues. The most effective treatment is assumingly obtained when one or two large doses are given in 24 hours — —as large as tolerated by the patient. Dr. Riska's experiments with one large dose of PAS are therefore of great interest as they give a blood concentration nearly as high as when PAS is given intravenously.

Alf Westergren, Sweden:

Just a few comments and implementary remarks on Stavenow's paper dealing with combined treatment and oversensitivity phenomena associated therewith. First, I would emphasize that combined treatment not only produces more favorable conditions with regard to resistance, but also a better direct clinical effect. I recall that results of such treatment were reported, apparently for the first time, in my communication at our Scandinavian congress in June 1946; and in several reports by Stavenow and myself in the following years it was shown that two drugs have a better action than one, and three drugs a better action than two. Logically, some further benefit might be gained by adding a fourth drug, at least insofar the resistance is concerned; and indeed this was our standard treatment at St. Göran's Hospital between 1952 and 1956. Various types of intolerance phenomena seemed, however. to become increasingly common. When Hillered on March 27th, 1957, presented a survey of these conditions before the Swedish Association of Phthisiologists I pointed out that I had adopted the procedure of giving initially only two two drugs, then adding the third and a fourth after intervals of two or three weeks. In this way it is sometimes easier, for instance, to find out if a particular drug is especially provocative.

At that meeting, as on several earlier occasions, I emphasized that these symptoms of intolerance are not to be equated with an allergic reaction, although connections with the latter are by no means absent; but among other things the phenomenon referred to by Stavenow today — namely, that sensitivity is often present to several drugs — seems to demonstrate that some factor associated with the tuberculous process itself is of fundamental significance. Sometimes we find, too, that the symptoms of intolerance are exacerbated at times of supervenient nonspecific infections. Further, the pronounced though transient reactive phenomenon which Stavenow has now discovered and which consists of a shift of the neutrophils to the left is, as far as I can see, more compatible with some sort of toxic reaction than with a pure allergic one.

Perhaps we could progress further in this field by giving chemotherapy of this kind to patients without tuberculosis.

EXPERIENCES WITH 527 SURGICALLY TREATED CASES OF PULMONARY TUBERCULOSIS[1]

By

O. Peräsalo, Hilkka Heikkilä and Terttu-Liisa Jalas

The results of follow-up studies in a series of 527 cases from the Helsinki Tuberculosis Sanatorium treated surgically in the period 1949—57 are presented.

Statistics on 273 patients subjected to thoracoplasty showed that, after an observation time of one and a half to eight years, the primary and secondary cures accounted for 71.2 % and those who were still ill for 15.9 %. Primary mortality was 2.5 %. Late tuberculous complications proved fatal in 8.6 %.

The data on 96 patients subjected to pneumolysis showed that, with an observation time varying from two and a half to eight years, the percentage of primary or secondary cures was 84.4 %. The proportion of patients still ill was 12.5 %. Primary surgical mortality was 2.1 % and mortality from late tuberculous complications 2.5 %.

The follow-up studies on 153 patients operated on by pulmonary resection showed that, after an observation time of six months to six years, the proportion of cures was 90.2 %, and the proportion of patients who were still ill 3.3 %. Primary mortality was 3.9 %, and the mortality from late tuberculous complications 2.6 %.

The different types of operation were compared, having regard to the various factors influencing the rate of relapse. The vital importance of sufficiently long pre- and postoperative medication is stressed. The relapse rate was found to be less after resections than after thoracoplasty or pneumolysis.

[1] This paper will be published in full in Ann. chir. et gynaec. Fenniae 1959 under the title "Relapses after Surgery for Pulmonary Tuberculosis". The present report is a summary of the paper.

FROM THE PAIMIO AND PIKONLINNA SANATORIA, FINLAND

THE RESULTS OF PNEUMOLYSIS

By

S. J. Viikari, V. Autio and P. Antila

Great advances have occurred during the last decade in the methods of treating pulmonary tuberculosis. Mainly responsible for this progress is the introduction of chemoantibiotics and resection therapy. As the number of optional methods of treatment has increased, a continued exchange of opinion concerning their value has resulted. Consequently the choice of the appropriate treatment may in some cases be much more difficult than it was ten to twenty years ago.

The writers of this paper have concurrently employed the three most customary methods, resection, thoracoplasty and pneumolysis, in the surgical treatment of pulmonary tuberculosis at two Finnish sanatoria (Paimio and Pikonlinna, 650 beds in all) during the period 1954—56. The distribution of surgical cases according to the type of surgery during this period is shown in Table 1.

TABLE 1.

Distribution of cases according to type of surgery in 1954—56

Thoracoplasty	110	cases	(30.0 %)
Resection	120	„	(32.7 %)
Pneumolysis	137	„	(37.3 %)
Total	367	cases	

As our experience has shown that the application of pneumolysis yields favorable results, we have considered it of interest to present a detailed survey of our cases. Most of the earlier studies in this field are from the period prior to the introduction of antibiotics, and for this reason we thought it worth while to evaluate the results of chemoantibiotic therapy in relation to pneumolysis.

Present Series

Since the introduction, in January 1954, of pneumolysis as a surgical method of treatment in the sanatoria mentioned, we had by the end of 1956 performed 138 pneumolyses on 137 patients. Of these patients 81 were men and 56 women. Their mean age was 30 years.

The choice of the most favourable time for performing pneumolysis is determined largely by the status of the disease. The time that had elapsed from the diagnosis of the disease to the operation is shown for the patients of our series in Table 2.

TABLE 2.

Interval from diagnosis of disease to pneumolysis operation

— ½ yr.	48 cases	(35 %)
½ — 1 yr.	36 „	(26 %)
1 — 2 yr.	12 „	(9 %)
2 — 3 yr.	15 „	(11 %)
3 — 5 yr.	12 „	(9 %)
5 — yr.	14 „	(10 %)

Mean 1.7 years

When evaluating the extent and localisation of the pulmonary involvement in each case, we have attempted to determine the bronchopulmonary segments in which the lesion has developed. Any attempt to localise pulmonary lesions by segments with the aid of roentgenologic methods is often difficult and may frequently lead only to a probable site. The decision is rendered particularly difficult by shrinkage and displacement of lung tissue. Though we are aware of these sources of error, we have nevertheless estimated the extent and localisation of the pulmonary lesions on the basis of the available roentgenologic information with the results shown in Tables 3 and 4.

TABLE 3.

Extent of tuberculous involvement before pneumolysis

Changes in one segment	35 cases	(25 %)
Changes in two segments	65 „	(47 %)
Changes in three segments	27 „	(20 %)
Changes in four segments	7 „	(5 %)
Changes in five segments	2 „	(1.5 %)
Changes in six segments	2 „	(1.5 %)

TABLE 4.

Location of cavity or primary focus of disease

Apical segment of upper lobe	47	cases	(34 %)
Posterior segment „	78	„	(56 %)
Anterior segment „	8	„	(6 %)
Superior segment of lower lobe	5	„	(4 %)

When seeking indications for pneumolysis, the size of the cavity is of decisive significance. We have never applied pneumolysis when the cavity exceeds 4 cm in diameter. Whenever it has not been possible to reduce the size of the cavity by treatment, resection has been resorted to. In Table 5 our patient material is shown classified according to the size of the cavity at the time the operation was performed. Changes in the contralateral lung were noted in 50 (36.5 %) of our patients.

TABLE 5.

Cavity size

Small cavities less than 2.5 cm in diameter	108 cases
Large cavities 2.5 to 4 cm in diameter	30 „

Chemoantibiotic Therapy in Conjunction with Pneumolysis

Antituberculotic drug therapy alone frequently cures pulmonary tuberculosis. On the other hand, this type of therapy has extended the range of application of surgery to cases in which it would have previously been considered impossible.

During the years 1954—55 we employed chemoantibiotic therapy of short duration prior to pneumolysis operations. When we prolonged the preparatory chemoantibiotic therapy, we observed that most cavities could be closed by conservative treatment. For this reason we extended in 1955—56 the duration of drug therapy to six months, and only if no definite signs of cavity closure were observed after this period was surgery instituted. In addition, drug therapy was continued during the collapse period so that in the later cases the whole duration of the drug therapy was one year and more.

The basic dosage was 14—16 g of PAS every day and in alternate months 1 g of streptomycin every other day or 5 mg of INH per kilogram body weight daily. It is now considered that this dosage generally is not fully adequate.

Indications for Pneumolysis

The indications for surgery have become apparent from the above. In general we have applied pneumolysis in the treatment of limited and fresh lesions. In such cases the cavity walls have still been sufficiently soft to permit closure by pneumolysis. Older cases where considerable connective tissue has formed within the lung cannot, in our opinion, be satisfactorily treated by reversible pneumolysis since the lung has a strong tendency to enter a state of permanent collapse. Difficulties are then encountered when pneumolysis is terminated, for fluid readily accumulates in the pneumolysis cavity.

In most of the cases the major focus of disease was located in the apicoposterior part of the upper lobe. There were, however, eight cases in our series in which the cavity was found in the anterior segment of the upper lobe. Favorable results were obtained in all these eight cases. In five cases the cavity was located in the superior segment of the lower lobe. Satisfactory results were also obtained in these five cases, allthough we have generally applied resection therapy when the cavity is in this segment.

Of particular importance is the location of the cavity in relation to the lung surface. Owing to the dangers associated with perforation, we have generally taken peripherally located cavities to be contraindications for pneumolysis. Nylander and Kivikanervo, for instance, consider the dangers of perforation to be greater when the lung has become strongly attached to the thoracic wall and blood vessels have penetrated into the lung tissue in the vicinity of the cavity. When this blood flow is terminated by pneumolysis, a nutritional disturbance develops in the lateral wall of the cavity, which may then rupture after a short period of time. Two cases of cavity rupture occurred in our series, which confirms this statement.

When the lung seems to have very strongly adhered to the thoracic wall we have not proceeded with pneumolysis, since detachment of the lung in such cases could have been too drastic.

Bronchial tuberculosis clearly revealed by bronchoscopy has also been recognised as a contraindication. A mild inflammation of the bronchial mucosa has been taken as an indication against the institution of pneumolysis. Definite bronchiectasis in the diseased area revealed by bronchography has also been a contraindication. Neither has pneumolysis been applied when distinct, large, round infiltrations (tuberculomas) have been evident; these have been removed by resection.

The adequacy of the respiratory reserves for the maintenance of collapse therapy has been evaluated before operation by spirometry and, when necessary, by bronchospirometry.

Surgical Technique and Postoperative Treatment

The operations have been performed with the patients in side position following endotracheal anaesthesia. The lung has been detached extrapleurally and medially until the hilus and the branching point of the upper lobe bronchus have been exposed. The pneumolysis cavity has been extended anteriorly approximately up to the level of the sternal insertion of the third rib and posteriorly to the level of the seventh or eighth rib. The magnitude of the pneumolysis has been varied according to the extent and location of the diseased area.

In cases where postoperative accumulation of blood into the pneumolysis cavity has been abundant and large haematomas have resulted (15 cases), the pneumolysis cavity has been entered a second time. The latter can well be done under local anaesthesia and does not tax the patient unduly. The results of the operation have been most gratifying in such cases.

A slight negative pressure has been maintained during the first three weeks after pneumolysis, but the pressure has been kept slightly positive later. The aim has been to effect reversible collapse. Pneumothorax has been maintained for a period of 1 to 2 years in all the patients, the mean period being about 18 months.

Complications

Previously pneumolysis was looked upon askance owing to the complications that usually followed it. Especially before the period of antibiotics there was great possibility that the extrapleural space became infected. An unspecific infection or a tuberculous empyema following the perforation of a cavity very often led to diappointing results.

The primary complications noted in the present series are listed in Table 6 and the late complications and their treatment in Tables 7 and 8.

TABLE 6.

Primary complications following pneumolysis

Rupture of pleura during operation	8	cases	(6 %)
Serious postoperative haemorrhage	15	„	(11 %)
Wound inflammation	2	„	(1.5 %)
Severe postoperative pneumonia	2	„	(1.5 %)
Rupture of cavity, specific empyema	2	„	(1.5 %)
Death from bilateral pneumonia	1	case	(0.7 %)

TABLE 7.

Late complications

Early expansion of lung	1 case	(0.7 %)
Unspecific empyema	1 „	(0.7 %)
Abundant exudate	16 cases	(12 %)

TABLE 8.

Cases where pneumolysis alone did not yield satisfactory results

On the side subjected to pneumolysis		11 cases	(8 %)
Resection	3 cases		
Thoracoplasty	1 case		
Active symptoms and under treatment	5 cases		
Died postoperatively	1 case		
Died later	1 case		
On the contralateral side		4 cases	(3 %)
Recestion	1 case		
Thoracoplasty	1 case		
Active symptoms; under treatment	2 cases		

s

Late Results

With a single exception the results of follow-up examinations were obtained for all of the treated patients. The extrapleural pneumothorax had in all cases been terminated prior to the follow-up examinations. The mean period of observations was three years. The results are listed in Table 9.

TABLE 9.

Follow-up examinations in the spring of 1958

No active symptoms; at work regularly	123 cases	(90 %)
Convalescent (tb —)	4 „	(3 %)
Active symptoms (tb +)	7 „	(5 %)
Dead	2 „	(1.5 %)
No information obtained	1 case	

Present Status of Pneumolysis

The alternative method of treatment that might have been undertaken instead of pneumolysis in our patients would frequently have been resection of a segment or a lobe. Thoracoplasty might also have been performed. A basis for deciding between the different methods is provided

by the loss of function that may be suspected to result. In this respect pneumolysis is no less favourable than the other methods of treatment.

Although a direct comparision of our thoracoplasty, resection and pneumolysis series is not possible, we have obtained our best results with pneumolysis. These results compare well with those obtained by others who have employed thoracoplasty and resection. When decided upon after proper deliberation, pneumolysis, in our opinion, well holds its own among the methods employed to combat pulmonary tuberculosis. The complications that beset pneumolysis as a method of treatment before the period of chemoantibiotics are now unusual and can be easily coped with.

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SERVICE MÉDICAL DE L'HÔPITAL MARIA, HELSINGFORS
CHEF: PROF. G. TÖTTERMAN

DÉTERMINATION DE LA DÉHYDROGÉNASE LACTIQUE DANS LES ÉPANCHEMENTS PLEURAUX

Par

LOUIS PERRET et TOR-MAGNUS ENARI

Plusieurs réactions enzymatiques ont déjà contribué au diagnostic clinique. Récemment *Felix Wroblewski* a insisté sur l'importance de l'enzyme déhydrogénase lactique, LD. Cette enzyme agit par une oxydation de l'acide lactique, CH_3.CHOH.COOH, qui le transforme en acide pyruvique, CH_3.CO.COOH.

L'existence de LD dans le sérum humain fut démontrée par *Warburg* et *Christian* en 1943 [3]. *Hill* et ses collaborateurs ont étudié l'activité de cette déhydrogénase dans le sérum dans des cas de tumeurs malignes.[2] Ils ont trouvé que le taux sérique de LD est toujours élevé en pareil cas. En outre, ils ont trouvé le taux de LD élevé dans le sérum de la femme enceinte.

De recherches semblables à celles de *Hill,* entreprises par *Wroblewski* et *La Due* ainsi que *Zimmerman* et *Weinstein* ont donné un taux sérique élevé dans la moitié seulement des cas de tumeurs malignes.[6]

Gordin et *Enari* ont montré des taux sériques élevés dans l'anémie de Biermer et dans l'anémie bothriocéphalique fréquemment observée en Finlande [1]. *Wroblewski,* ayant étudié l'activité de LD dans le sérum, dans le liquide céphalorachidien et dans des divers épanchements de l'organisme, a présenté une communication préliminaire de ses résultats au congrès international de chimie clinique à Stockholm en 1957 [4]. Il insistait sur le fait qu'un épanchement dû à un processus de nature maligne présente un taux plus élevé de LD que le sérum du même malade. Par contre, un exsudat infectieux présente un taux de LD inférieur à celui du sérum.

A partir de ces observations de *Wroblewski,* nous avons fait une série de déterminations de l'activité de LD dans quelques cas de pleurésie carcinomateuse et de pleurésie infectieuse. Les cas ont été obtenus du service médical de l'Hôpital Maria, de la IV clinique médicale universitaire, de l'Institut universitaire de Radiothérapie, du sanatorium de la ville Helsingfors et de l'Hôpital Aurora à Helsingfors. Nous tenons à exprimer nos rémerciements sincères aux chefs de ces cliniques pour leur appui bienveillant.

La détermination de l'activité de LD a été faite au laboratoire de l'Hôpital Maria à l'aide d'un appareil spectrophotométrique du type Beckman-DU, selon la méthode préconisée par ***Wroblewski*** et ***La Due*** en 1955 [5]. Selon cette méthode le taux sérique normal varie entre 200 et 680 unités. ***Enari*** a trouvé un taux sérique moyen inférieur à 350 unités et, en général, ses déterminations ont donné des taux inférieurs à ceux de Wroblewski. Ce qui nous intéresse en particulier, c'est la différence entre le taux de LD dans l'épanchement pleural et le taux sérique de LD. Cette différence donne ainsi une sorte "d'index" qui peut réveler s'il s'agit d'un processus malin ou non.

Nous avons jusqu'ici étudié 20 cas de pleurésies, dont 12 pleurésies carcinomateuses et 8 pleurésies infectieuses. Les causes des 12 pleurésies carcinomateuses se repartissent ainsi: Cancer du poumon (3 cas), cancer du sein (6 cas), cancer de l'estomac (1 cas), cancer du pancréas (1 cas), cancer du colon transverse (1 cas). Dans le douzième cas le diagnostic n'a pu être confirmé.

Dans les 8 cas de pleurésis infectieuses, 1 cas présentait un épanchement hémorragique dû à un infarctus pulmonaire surinfecté, confirmé par autopsie. Dans 3 cas on a trouvé des bacilles de Koch, tandis que dans les autres 4 cas le diagnostic s'était basé sur le développement clinique qui militait en faveur d'une pleurésie tuberculeuse.

Le tableau 1 expose les 20 cas et leur diagnostic le taux de l'activité de LD dans l'épanchement pleural et dans le sérum ainsi que la différence entre les taux obtenus. La figure 1 montre la distribution des cas selon la différence entre les taux de LD. Tous les 12 cas de pleurésies carcinomateuses qui ont un taux de LD plus élevé dans l'épanchement pleural que dans le sérum, et donc une différence positive, sont groupés à droite du point zéro, tandis que les résultats concernant les pleurésies infectieuses sont plus incertaines. 5 des 8 cas de pleurésies infectieuses sont groupés à gauche du point zéro, 2 cas sont tout près de ce point, et un cas présente une différence positive de 710, un résultat sans doute déconcertant.

Le cas no 4, une femme de 61 ans avec un épanchement pleural droit provenant d'un cancer du colon transverse avec métastases pulmonaires mérite d'être brièvement commenté. Des cellules tumorales furent rencontrées dans l'épanchement et un traitement par de l'or radioactif, Au 198, fut institué le 17. 12. 1957. Deux semaines plus tard une détermination de LD fut faite: le taux de LD dans l'épanchement était 133 unités et

o = *pleuritis.maligna*
x = *pleuritis infectiosa*

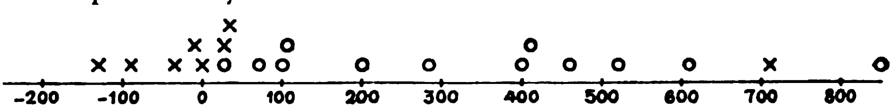

Fig. 1.

TABLEAU 1

	Diagnosis	LD activity pleural effusion	LD activity serum	Difference
1	Ca. pulm. sin.	450	250	200
2	Ca. pulm. dx? Pleuritis exs. l. dx.	683	283	400
3	Ca. mammae sin. op. cum metast. pleur.	950	100	850
4	Ca. coli cum metast. pulm. et periton.	420	132	288
5	Ca. ventriculi op. cum metast. pleur.	855	445	410
6	Ca. pancreatis op. cum metast. pulm.	467	366	101
7	Ca. mammae dx. op. cum metast. pulm.	353	247	106
8	Ca. mammae dx. op. Pleuritis l. sin.	207	136	71
9	Ca. pulm. sin.	194	167	27
10	Ca. mammae sin. op. cum metast. pleurae dx.	670	150	520
11	Ca. mammae dx. non rad. op. Pleuritis l. dx.	840	230	610
12	Ca. mammae sin. inop. cum metast. cutis	1140	680	460
13	Pleuritis exs. l. sin.	870	160	710
14	Pleuritis haemorrhagica. Infarctus pulm.	113	243	—130
15	Pleuritis exs. l. sin.	183	156	27
16	Tub. cavernosa pulm. dx. Pleuritis exs. l. dx.	200	200	0
17	Pleuritis exs. l. sin.	190	200	—10
18	Tub. pulm. dx. Pleuritis exs. l. dx.	466	500	—34
19	Tub. pleurae dx.	210	300	—90
20	Peluritis exs. l. dx.	260	220	40

le taux sérique 190. L'activité de LD dans le liquide pleural était donc inférieur à celle du sérum, un résultat probablement dû à l'effet cytostatique de l'or radioactif. Le malade, le service, fut réhospitalisée le 13. 2. 1958 avec un processus métastatique avancé et un nouveau épanchement à gauche, qui n'avait été traité par de l'or radioactif ou d'autre remède cytostatique. Une nouvelle détermination de l'activité de LD dans cet épanchement donnait un taux plus élevé dans l'épanchement, 420 unités, que dans le sérum, 132 unités. Le diagnostic d'un cancer du colon transverse avec métastases pulmonaires et péritonéales fut confirmé par autopsie.

Conclusions. Un taux de LD plus élevé dans l'épanchement pleural que dans le sérum d'un malade atteint d'une pleurésie d'étiologie inconnue indique selon toute vraisemblance un processus de nature maligne. La différence entre les taux de LD dans l'épanchement pleural et le sérum doit pourtant être suffisamment accusée, environ 70—100. La poursuite de nos recherches montrera dans le plus proche avenir si cette méthode peut être employée comme un des tests habituels du diagnostic différentiel des pleurésies.

SUMMARY

Based on a report by F. Wroblewski concerning LD activity in serous effusions and in serum from the same individual, the authors examined 20 cases of pleural effusion, 12 of them due to malignant tumours and 8 due to bacterial infection as shown in table 1. A precise diagnosis failed in 1 case of the "malignant" group and in 3 cases of the "infectious" group. In the former group all 12 cases presented a greater LD activity in pleural effusion than in serum, in the infectious group only 5 had a greater (in 1 case the same) LD activity in serum than in pleural effusion. The difference between the units of activity was smaller in the infectious group with the exception of 1 case. The distribution of the two groups of pleural effusion is shown in Fig. 1.

Case nr 4 with a pleural effusion on the right side, due to cancer of the colon with pulmonary metastases, was treated with radioactive colloidal gold, Au 198. Two weeks later the determination of LD activity showed a lower activity in pleural effusion, 133 units, than in serum, 190 units, unless cancer cells were found in the pleural fluid. 6 weeks later the patient got a pleural effusion on the left side; this was not treated with radiogold and here LD activity was again greater in the pleural effusion, 420 units, than in serum, 132 units. As pointed out by Wroblewski, radiation and cytostatic therapy may result in enzymatic change in serous fluid, presumably the LD activity diminish, when the malignant process comes to a stillstand. Further experience soon will show if the spectrophotometric determination of LD activity can be used as a routine test in the differential diagnosis of pleurisy, especially in case of pleurisy of unknown etiology in older persons.

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